

Chapter 1

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- 📖 Define atheroma, explain its pathogenesis, describe its pathologic features, list its risk factors and complications.
- 📖 Compare and contrast between stable and unstable plaques.
- 📖 Define hypertension, list its predisposing factors and explain its pathogenesis.
- 📖 Compare between the vascular changes in benign and malignant hypertension.
- 📖 Identify types of aneurysms and list complications.
- 📖 Define vasculitis, list its types and explain pathogenesis.
- 📖 Classify congenital heart diseases and explain their pathogenesis and possible complications.
- 📖 Describe the pathologic features, clinical manifestations and complications of myocardial infarction.
- 📖 Analyse and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.
- 📖 Define rheumatic fever, explain its pathogenesis and describe the pathologic features and list its complications.
- 📖 Describe the pathologic features of acute and chronic rheumatic valvulitis.
- 📖 Compare and contrast between acute and subacute bacterial endocarditis.
- 📖 Describe the pathologic features of the different types of endocarditis.
- 📖 Define calcific aortic stenosis, describe its pathologic features and list its complications.
- 📖 Compare and contrast between different types of cardiomyopathy.
- 📖 Define and classify myocarditis.
- 📖 List causes of pericarditis and describe the pathologic features of chronic pericarditis.
- 📖 Classify tumours of the heart.

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Diseases of the Blood Vessels

Congenital and developmental anomalies of the blood vessels:

- 1- **Developmental or berry aneurysms** occur in cerebral vessels.
- 2- **Arteriovenous fistulas** are abnormal, small direct connections between arteries and veins that bypass the intervening capillaries.
- 3- **Fibromuscular dysplasia** is a focal irregular thickening of the walls of medium and large muscular arteries, including renal, carotid, splanchnic, and vertebral vessels. The cause is unknown but is probably developmental.

Degenerative diseases of the blood vessels (Arteriosclerosis):

Arteriosclerosis literally means "hardening of the arteries"; it is a generic term reflecting arterial wall thickening and loss of elasticity.

Three patterns are recognized, with different clinical and pathologic consequences.

1- **Arteriolosclerosis:**

- It affects small arteries and arterioles.
- Hyaline and hyperplastic arteriolosclerosis, will be described in relation to hypertension.

2- **Mönckeberg medial calcific sclerosis:**

- This is a degenerative disease of unknown cause characterized by dystrophic calcification of the media.
- It is common in muscular arteries in elderly people.
- The disease produces no clinical effects because the lumen is not narrowed.

3- **Atherosclerosis:**

- Atherosclerosis is from Greek root words for "hardening".
- It affects mainly large and medium sized arteries.
- It is characterized by intimal lesions called atheromas (also called atheromatous or atherosclerotic plaques) that protrude into vascular lumina.

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Atheromatous plaque

- It consists of a raised lesion with a soft, yellow core of lipid (mainly cholesterol cholesterol esters) and covered by a firm white fibrous cap.
- It is the most frequent and clinically important arterial disease.
- Atherosclerosis causes more morbidity and mortality (roughly half of all deaths) in Western world than any other disorder. It is manifested as:
 - a- Coronary artery disease.
 - b- Carotid atherosclerotic disease and stroke.

Risk Factors for atherosclerotic arterial disease

- 1) Increasing age: Significant disease is rare under 30 years of age.
- 2) Lack of physical exercise and stressful life patterns.
- 3) Sex: Males are affected more than females. Female incidence increases after the menopause.
- 4) Family history of ischemic heart disease in a patient or a sibling under the age of 55 years.
- 5) Hyperlipidemia: Is the major risk factor in patients under 45 years of age. It may be due to genetic defects or secondary to other diseases as nephrotic syndrome, diabetes, hypothyroidism or high fat intake.
NB: Any increase in LDL (low density lipoprotein) content of plasma increases the risk for atherosclerosis but increase in plasma HDL (high density lipoprotein) is protective against atherosclerosis (as in premenopausal females).
- 6) Hypertension: The major risk factor in patients over 45 years of age.
- 7) Cigarette smoking: Ten cigarettes per day increases the risk three folds. Cessation of smoking decreases the risk to normal after 1 year.
- 8) Diabetes mellitus: Both type I and type II diabetes mellitus are associated with two fold increase in risk.

NB: The risk factors impose more than a simple additive risk.

Pathogenesis of atherosclerosis

The mechanism responsible for lipid deposition in the intima and formation of atheromatous lesions is unknown. The following theories are to be considered (Fig.1.1).

A) Reaction to endothelial injury -

1. Non-denuding endothelial injury is believed to lead to adherence of blood monocytes which are activated, imbibe LDL and actively enter the intima and become macrophages.

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2. Active macrophages release free radicals that oxidise LDL. The oxidised LDL is toxic to endothelium causing endothelial loss and exposure of subendothelial connective tissue to blood components. This leads to platelet adhesion forming microthrombi.
3. Platelets release various factors one of which has been identified as being mitogenic causing migration of smooth muscle into the intima and proliferation there.
4. Activated macrophages and smooth muscle cells secrete numerous cytokines e.g. platelet derived growth factor (PDGF), tumour necrosis factor (TNF), fibroblast growth factor (FGF) and interleukin 1, some of which may also have mitogenic capability.
5. The smooth muscle cells, macrophages and matrix accumulate LDL from the plasma, a process that is enhanced by the presence of increased LDL in the blood. Smooth muscle cells and endothelial cells have LDL receptors on their surfaces.

NB: The nature of the initial endothelial injury is unknown: Physical tear injuries are maximal at sites of arterial branching which are the sites most involved.

B) Thrombus encrustation theory:

- It states that small thrombi collected over foci of endothelial injury and the organization of such thrombi resulted in plaque formation.
- The lipid here is derived from the breakdown of platelets and leucocytes rather than serum lipoproteins.
- Endothelial injury may be due to: aging process, hypertension, viruses, stress, cigarette smoking or immune complex deposition.

NB: Thrombosis is now thought not to be the initial event but it probably plays a role in the development and enlargement of the lesion.

Pathologic features of atherosclerosis:

The lesions of atherosclerosis are:

- 1- Fatty streaks
- 2- Fibrous atheromatous plaque (*Fig.1.2 & 1.3*).
- 3- Acute plaque changes (complicated lesion) (*Fig.1.4*).

The latter two are responsible for clinically significant disease.

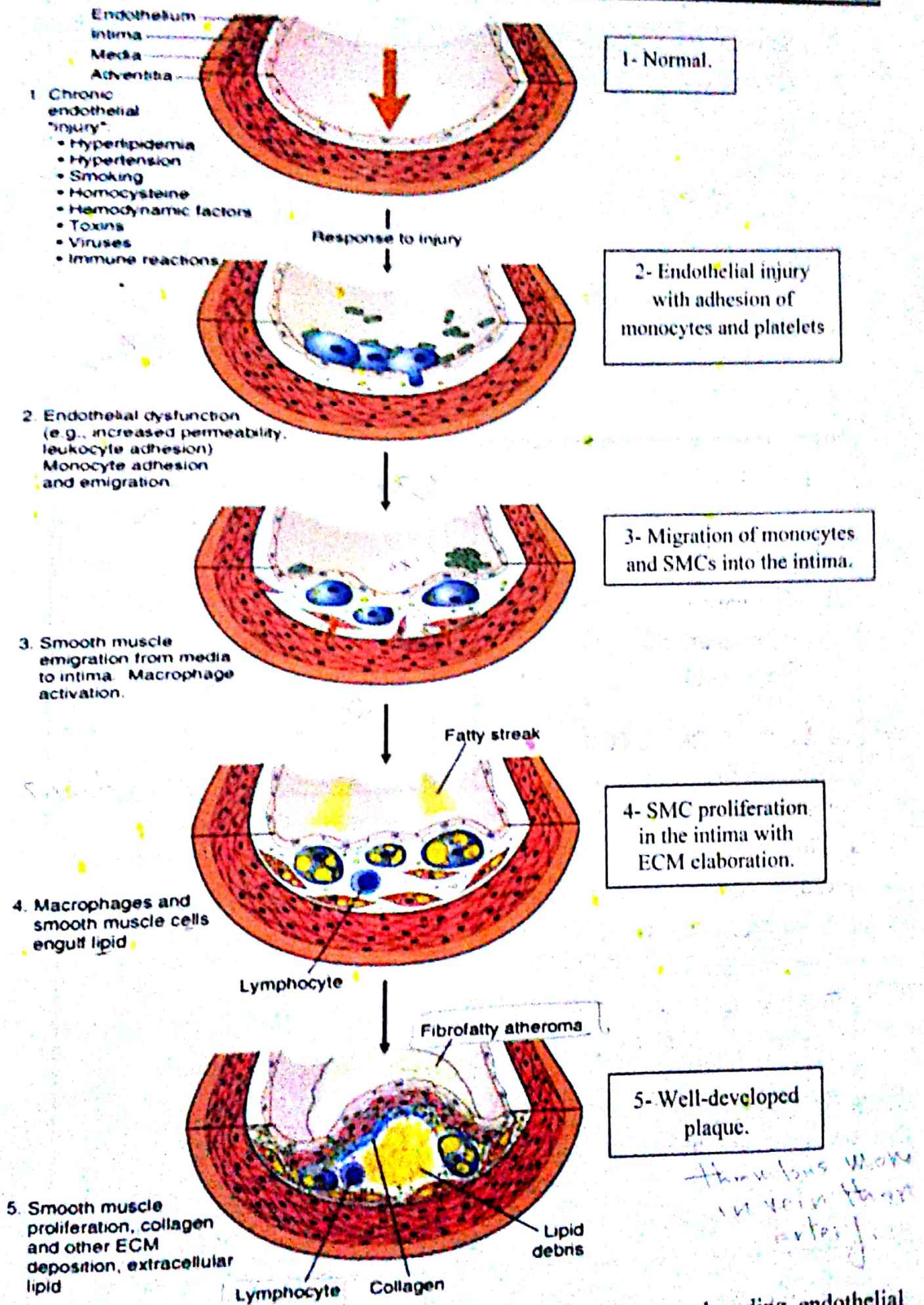


Fig.1.1: Atherosclerotic arterial wall changes in response to non-denuding endothelial injury hypothesis.



Fig. 1.2: Severe complicated atherosclerosis

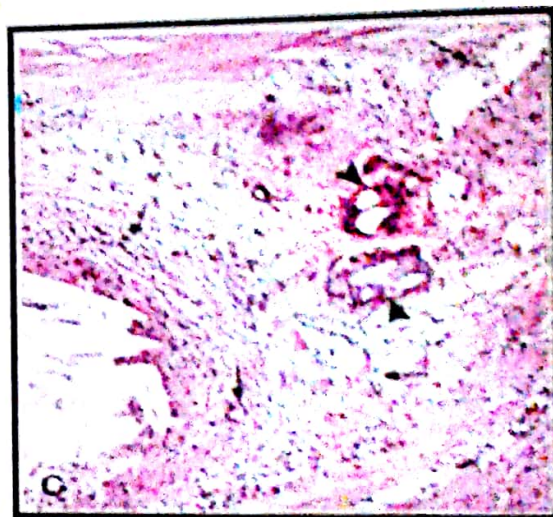


Fig. 1.3: A: Fibrous cap (F), central necrotic lipid core (C), lumen (L)
B: Scattered inflammatory cells & calcification (arrow head)

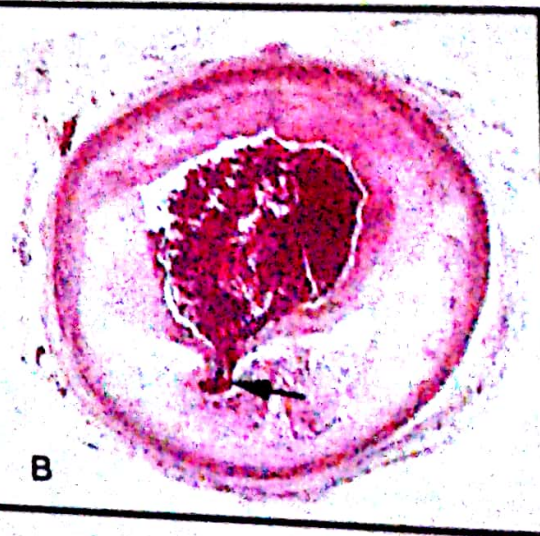
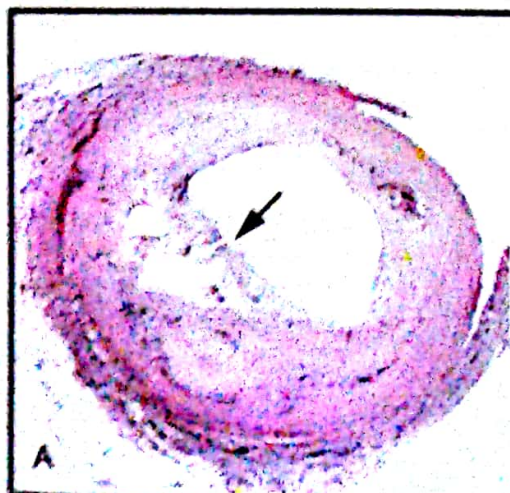


Fig. 1.4: A: Plaque rupture (arrow).
B: Acute coronary thrombosis on an atherosclerotic plaque with focal disruption of the fibrous cap (arrow).

A. Fatty streaks:

They are thin, flat, yellow streaks in the intima, very hard to be seen macroscopically but can be stained with Sudan III.

Sites: They occur maximally around the aortic valve ring and thoracic aorta.

Microscopic: They consist of macrophages and smooth muscle cells whose cytoplasm is distended with lipid to form foam cells.

- They are present very early in life, often in the first year irrespective of sex, race or environment.
- They increase in number until about the age of 20 years and then remain static or decrease.
- There is controversy about whether some fatty streaks progress into fibrous atheromatous plaques or whether they are independent of atherosclerosis.

B. Fibrous atheromatous plaque:

This is the basic lesion of clinical atherosclerosis.

Gross: It appears as yellow-white elevation on the intimal surface of the artery. The centre of the plaque consists of semisolid yellow material.

Sites:

- In the aorta and most commonly in the abdominal aorta.
- Involvement of muscular arteries such as the coronary, carotid, vertebrobasilar, mesenteric, renal and iliofemoral arteries and is associated with luminal stenosis.
- Plaques tend to be most prominent at points of branching of the major arteries.
- In severe disease plaques become confluent.

Microscopic:

It consists of three zones which vary in thickness in different plaques

1. **Fibrous cap** under the endothelium, consisting of dense collagen, scattered smooth muscle cells and macrophages.
 2. **The lipid zone**, consists of foam cells (lipid laden macrophages and smooth muscle cells), extracellular lipid, cholesterol crystals and necrotic debris.
 3. **The basal zone**, composed of smooth muscle cells and connective tissue.
- Vascularization of the plaque occurs by ingrowth of poorly supported vessels from the media.
 - Different plaques contain varying amounts of these three layers, some are mainly fibrous and others are predominantly fatty.
 - Dystrophic calcification is common and occurs in the lipid zone.

C. Acute plaque changes:

- Plaque rupture causes acute catastrophic vessel thrombosis.
- Thrombosis cause complete occlusion of the artery.
- Ulceration of the endothelium overlying the plaque may cause the lipid contents of the plaque to be discharged into the circulation as cholesterol emboli.
- It may also precipitate thrombosis over the ulceration.
- Haemorrhage into the atheroma that may expand its size sufficiently to occlude the lumen of the artery.
- Haemorrhage may cause also ulceration and thrombosis.

Effects and complications of atherosclerosis (Fig.1.5):

1. The Aorta

- Weakening of the wall with dilatation i.e. atheromatous aneurysm.
- Mural thrombosis may occur with detachment and embolic manifestations.

2. In the medium sized vessels:

- Narrowing of the lumen leading to ischaemia.
- Complete occlusion leading to cut of blood supply (infarction)

These may be due to thrombosis, haemorrhage or ulceration of the plaque.

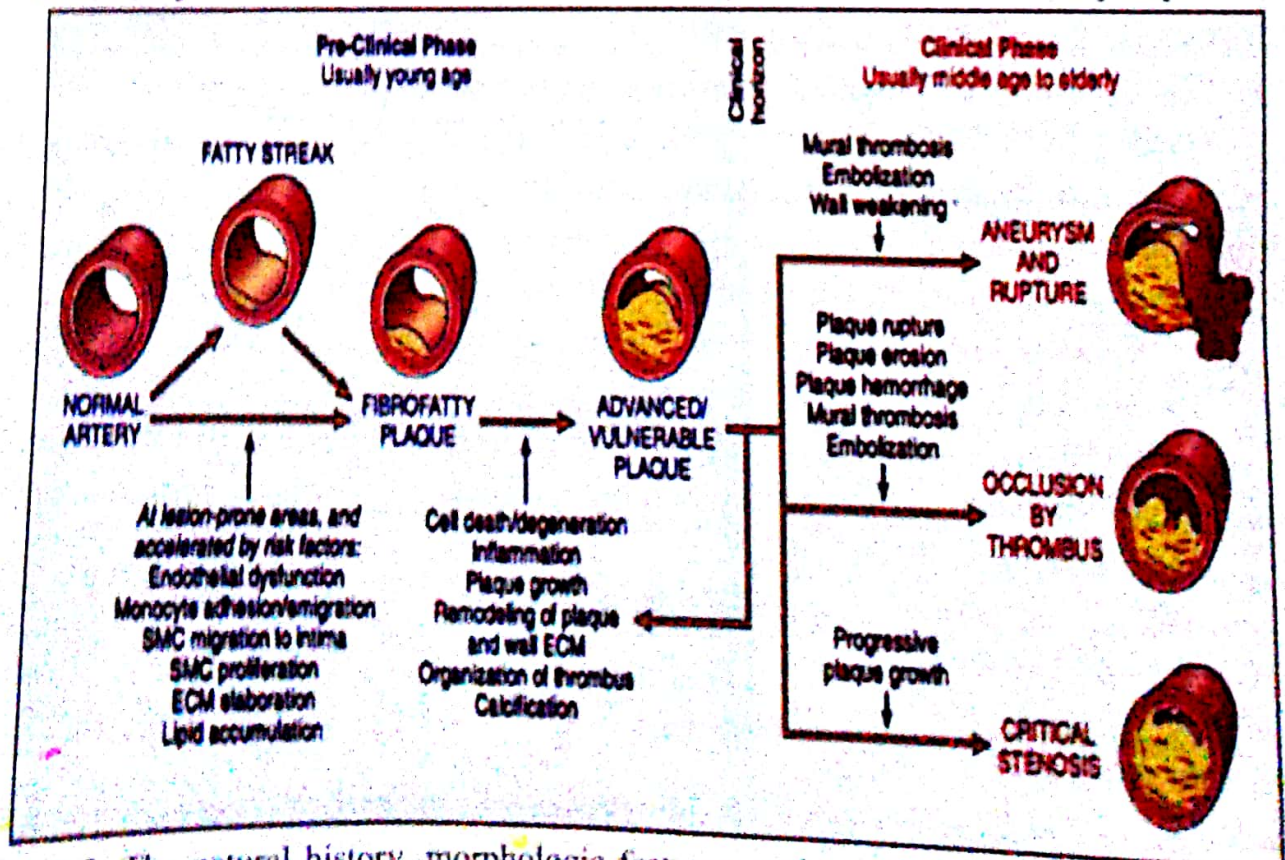


Fig.1.5: The natural history, morphologic features, main pathogenic events and clinical manifestations of atherosclerosis

Hypertension or arteriolosclerosis:

It is a permanent elevation of the blood pressure above 140 mm Hg (systolic) and 90 mm-Hg. (diastolic).

Classification of systemic hypertension:

- 1- According to the cause hypertension is classified into:
 - [A] Primary, essential or idiopathic (without a known cause).
 - [B] Secondary or renal.
- 2- According to the severity and course; hypertension (primary, secondary) is classified into "benign" and "malignant".

[A] Primary or essential or idiopathic hypertension.

- It is the commonest type (95%), occurring after the age of 40 years.
- It is either benign (95%) or malignant (5%).

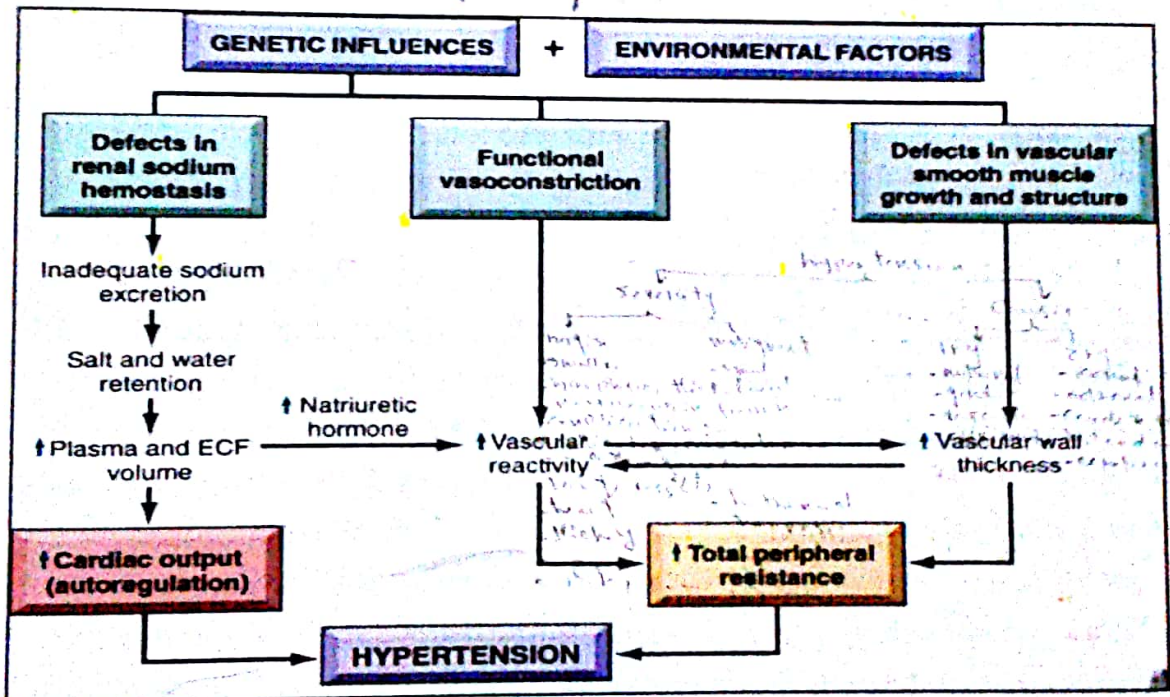


Fig.1.6: Pathogenesis of essential hypertension

Pathogenesis of essential hypertension:

- 1- The pathogenesis is uncertain. It is proposed to be due to *high dietary intake of sodium in a genetically predisposed individual*.
- 2- Genetic factors;
 - **Gene defect in enzymes involved in aldosterone metabolism;** leading to **increased aldosterone secretion**, **increased salt and water resorption** and **plasma volume expansion**.

- Mutations in proteins that affect sodium resorption; leading to increased distal tubular resorption of sodium.
- 3- Increased vascular resistance may stem from vasoconstriction or structural changes in vessel walls.
- 4- Environmental factors, such as stress, obesity, smoking, physical inactivity, and high levels of salt consumption, modify the impact of genetic determinants (Fig. 1.6).

[B] Secondary hypertension (5%):

- It is secondary to a pre-existing disease, commonly renal (renal hypertension).
- It is either benign (80%) or malignant (20%).

Causes:

(1) Renal diseases such as:

- ☐ Chronic pyelonephritis.
- ☐ Chronic glomerulonephritis.
- ☐ Diabetes mellitus.
- ☐ Polycystic disease of the kidney.
- ☐ Renal amyloidosis.
- ☐ Some renal tumours.
- ☐ Connective tissue diseases particularly polyarteritis nodosa.
- ☐ Toxaemia of pregnancy.

(2) Adrenal-mediated hypertension:

- ☐ Conn's syndrome (Primary hyperaldosteronism).
- ☐ Cushing's syndrome (ACTH).
- ☐ Pheochromocytoma (Catecholamine secreting neoplasm).

(3) Diseases of cardiovascular system:

- ☐ Coarctation of the aorta.
- ☐ Arteriovenous shunts.

(4) Cerebral diseases:

- ☐ Increased intracranial tension due to trauma, tumours, haemorrhage.

(5) Blood diseases: especially polycythaemia.

Morphological changes in the blood vessels in hypertension

(Hypertensive arteriosclerosis)

- ♦ The changes occurring in small vessels, particularly the arterioles, are different in benign and malignant types of hypertension.

- ◆ In the large and medium-sized arteries, the vascular changes are the same in benign and malignant hypertension.
 - Hypertension accelerates atherogenesis.
 - Hypertension causes degenerative changes in the vessel walls that can lead to aortic dissection and cerebrovascular hemorrhage.

Benign hypertension:

- It is a very common disease which occurs above 50 years.
- It is characterized by a slowly progressive rise (in years) in blood pressure (below 200/100).

The essential organs affected are:

- (1) **Heart** (hypertensive heart): The left ventricle undergoes concentric hypertrophy (walls and septum) in response to the resistance of elevated blood pressure; walls of left atrium become also hypertrophic.
- (2) **Kidneys** (arteriolosclerotic kidney): or benign nephrosclerosis or primary contracted kidney (see chapter of kidney diseases).
- (3) **The affected small arteries and arterioles**, particularly those of the kidney show **hyaline**. It is marked by homogeneous, pink hyaline thickening of the arteriolar walls, with loss of underlying structural details, and luminal narrowing (*Fig. 1.7a*).

NB: Although the vessels of elderly normotensive patients show the same changes, hyaline arteriolosclerosis is more generalized and severe in patients with hypertension. The same lesions are also common in diabetics.

Causes of death:

1. Congestive heart failure (45%) due to increased work load thrown on the left ventricle.
2. Coronary insufficiency or infarction (45%).
3. Cerebro-vascular accident mainly cerebral haemorrhage (5%).
4. Renal failure (5%).

Malignant hypertension:

- It is a rare disease affecting mainly young adults
- It is characterized by a rapidly progressive form of hypertension reaching high levels e.g. 280/180 mmHg.
- It is accompanied by:
 - Severe headache.
 - Eye changes; retinal haemorrhages, exudates and papilloedema.
 - Severe impairment of the renal function with albuminuria.

Microscopic vascular changes in malignant hypertension:

The affected small arteries and arterioles in the body particularly those of the kidney show the following changes:

- 1- **Hyperplastic arteriolosclerosis:** Vessels exhibit "onion-skin," concentric, laminated thickening of arteriolar walls and luminal narrowing. The laminations consist of smooth muscle cells and thickened reduplicated basement membrane. (Fig. 1.7b).
- 2- **Fibrinoid necrosis** of the walls of arterioles and smallest arteries. The vessel walls show a homogenous granular eosinophilic appearance, due to permeation of the necrotic tissue by plasma constituents (Fig. 1.7c).

N.B.: Malignant nephrosclerosis: when the glomerular afferent arteriole is affected; the fibrinoid necrosis may extend into the glomerulus and rupture of capillaries may cause haematuria and produce visible *flea bite haemorrhages on the surface of the kidney*: (see chapter of kidney diseases).

The heart is usually within normal size.

Causes of death: The disease is serious and of poor prognosis.

- (1) Renal failure 95%.
- (2) Cerebro-vascular accidents mainly cerebral haemorrhage.
- (3) Coronary insufficiency.
- (4) Heart failure.

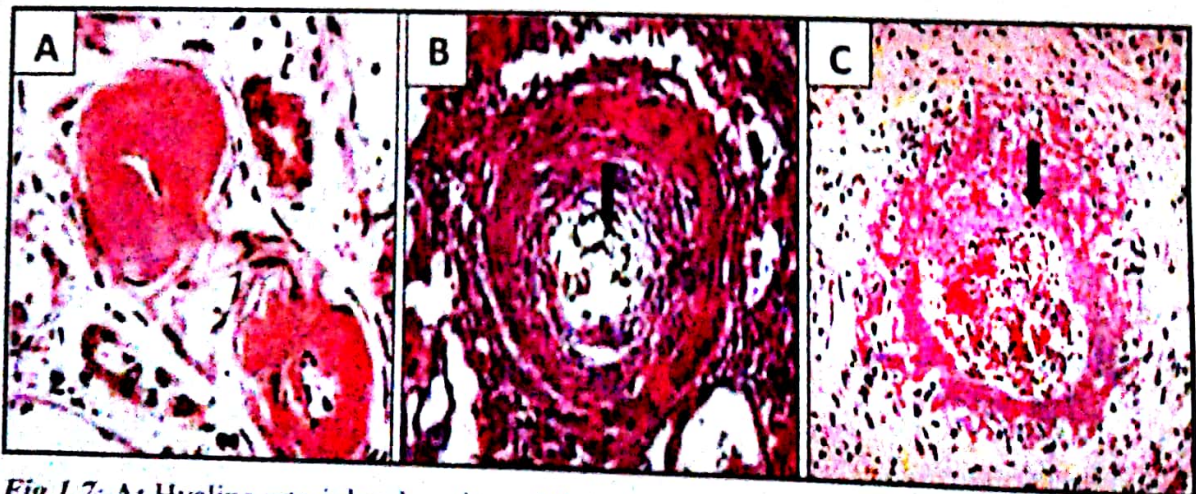


Fig.1.7: A: Hyaline arteriosclerosis, wall is hyalinized, lumen is narrowed.
B: Hyperplastic arteriosclerosis (onion-skin), luminal obliteration (arrow) PAS stain.
C: Fibrinoid necrosis (arrow)

Inflammatory diseases of arteries:

(Vasculitis or Angitis):

Pathogenesis of vasculitis:

1- Immune mediated (Non-Infectious) vasculitis (Table 1.1):

a- Immune complex mediated as:

- Systemic lupus erythematosus (SLE).
- Drug hypersensitivity vasculitis (e.g., penicillin).
- Vasculitis secondary to infections (e.g., some cases of polyarteritis nodosa in hepatitis B patients).

b- Anti-neutrophil cytoplasmic antibody (ANCA) as:

- Wegener granulomatosis

c- Anti-endothelial cell antibody as:

- Kawasaki disease.

2- Infectious vasculitis:

a- Direct invasion of vascular walls by infectious pathogens (bacteria).

The inflammation is usually localized to a segment of an artery.

b- Infections can also indirectly induce a noninfectious vasculitis, by generating immune complexes or triggering cross-reactivity.

NB: It is critical to distinguish between infectious and immunologic mechanisms, because immunosuppressive therapy is appropriate for immune-mediated vasculitis but could exacerbate infectious vasculitis.

3- Physical and chemical injury, such as irradiation, mechanical trauma and toxins can cause vasculitis.

Effects:

- 1- Ischaemic changes and infarction may occur.
- 2- Rupture of the artery leading to secondary haemorrhage.

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Table.1.1: Morphological features of Immune-Mediated Vasculitis

Type	Examples	Description
Large to small Vessel Vasculitis	1-Giant-cell (temporal) arteritis. Temporal, vertebral ophthalmic & aorta 2-Takayasu arteritis; Affects aortic arch & its branches 3-Kawasaki disease	- Granulomatous inflammation; involves the temporal artery, common in males over 50. There is infiltration by chronic inflammatory cells, foreign body giant cells, fibrosis and thickening of the wall, narrowing of the lumen and thrombosis may occur. - Type IV hypersensitivity against arterial wall - Granulomatous inflammation usually occurring in patients younger than age 50 Mucocutaneous lymph node syndrome. Segmental necrotizing vasculitis of infants & young children.
Medium-Vessel Vasculitis	Polyarteritis nodosa -Affects small or medium-sized arteries. -Typically involve renal, GIT arteries & spare pulmonary vessels	Causes: Type III hypersensitivity immune complex reaction. o HBS antigen is present in 30-40 % of cases. Gross: The arteries show nodular swellings along their course with aneurysmal dilatations. Microscopic: Segmental necrotizing vasculitis. - Early (fibrinoid necrosis) and infiltration of the wall with PNL. - Then chronic inflammation with fibrosis. - Aneurysm formation. Clinically; Fever of unknown cause, hypertension & abdominal pain. Thrombosis causing infarctions. Rupture of aneurysm causing hemorrhage
Small-Vessel Vasculitis (Arteriole, Venules, Capillaries and occasional small arteries)	1-Wegener granulomatosis 2-Churg-Strauss syndrome 3-Microscopic Polyangiitis	1. Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis of small vessels. Associated with c-ANCA 2. Eosinophil-rich granulomatous inflammation of respiratory tract and necrotizing vasculitis of small vessels. Associated with asthma, blood eosinophilia p-ANCA. 3. Necrotizing small-vessel vasculitis with few or no immune deposits; necrotizing arteritis of small and medium-sized arteries can occur. - Necrotizing glomerulonephritis and pulmonary capillaritis are common. Associated with p-ANCA.

c- ANCA: Antineutrophil cytoplasmic antibodies-cytoplasmic localization
p- ANCA: Antineutrophil cytoplasmic antibodies-perinuclear localization

Distinctive type of vasculitis:

Thromboangitis obliterans (Buerger's disease):

It is a segmental inflammatory condition of small and medium sized arteries with thrombosis, predominantly affecting the upper and lower limbs.

Microscopic: acute and chronic inflammation accompanied by thrombosis, which may undergo organization and recanalisation. The thrombus contains microabscesses and surrounded by granulomatous inflammation.

The inflammatory process extends into contiguous veins and nerves, and finally all three structures become encased in fibrous tissue.

Aetiology:

Unknown, but it is common in *heavy tobacco smokers* :

- Direct endothelial cell toxicity by some components of tobacco.
- Tobacco-induce immune response.
- Genetic predilection.

Clinical features and effects:

- 1- The early manifestations are cold sensitivity in the hands and pain in the instep of the foot induced by exercise (instep claudication). Pain may occur at rest due to neural involvement.
- 2- Trophic skin ulcers.
- 3- Gangrene of the limb is the end result.

Aneurysm

Aneurysm is an abnormal permanent localized dilatation of an artery, vein or heart. It is either true or false.

A- True aneurysm:

Its wall is formed by one or more layers of the affected vessel.

Aneurysms can be classified by shape into:

- Fusiform aneurysm: or diffuse dilatation affecting a segment of the artery taking the whole circumference.
- Saccular aneurysm: or localized dilatation affecting a part of the circumference to produce a globular sac.

Etiological types of true aneurysm (Fig.1.8):

(1) **Congenital aneurysm:** It occurs mainly in the arteries of the circle of Willis at the base of the brain.

Effects: If rupture, they can cause fatal intracerebral hemorrhage.

(2) **Atheromatous aneurysm:** It is the commonest type and occurs mainly in old people. It is of the fusiform type and affects mainly the abdominal aorta and common iliac arteries.

Effects: a- Pressure on the surrounding organs.
b- Rupture leading to fatal haemorrhage.
c- Thrombosis and embolism.

(3) **Syphilitic aneurysm:** It is usually saccular in shape. It occurs mainly in the ascending and transverse parts of the arch of the thoracic aorta.

Effects: a- Pressure on the trachea and oesophagus.
b- Erosion of the sternum by pressure necrosis with the production of pulsatile subcutaneous swelling.
c- Rupture with fatal haemorrhage.
d- Thrombosis and embolism.

(4) **Mycotic aneurysm:** It is due to weakness of the wall due to bacterial infection. Nearly all are associated with infective endocarditis. It is also seen in the walls of tuberculous cavities and abscesses. Commonest sites are coronary, cerebral, and mesenteric arteries.

Effects: Thrombosis - rupture (late).

(5) **Aneurysm of polyarteritis nodosa.**

(6) **Microaneurysms:** commonly seen in hypertension and diabetes.

B- False aneurysm:

Its wall is formed by connective tissue which is not part of a vessel wall.

Types:

- (1) **Pulsating haematoma:** It results from a small perforation in the wall of an artery due to trauma. The walls of haematoma are formed by the compressed adjacent tissue e.g. muscle and fascia.
- (2) **Arteriovenous fistula:** Is an abnormal direct connection between arteries and veins that bypass the intervening capillaries, it may be:
 - Developmental.
 - Traumatic rupture of an arterial aneurysm into the adjacent vein, from penetrating injuries that pierce arteries and veins.
 - Inflammatory necrosis of adjacent vessels.
 - Iatrogenic (surgically) created arteriovenous fistulas which are used to provide vascular access for chronic hemodialysis.

Complications:

- **High-output cardiac failure** may occur in large arteriovenous fistulas due to shunting of blood from the arterial to the venous circulation.

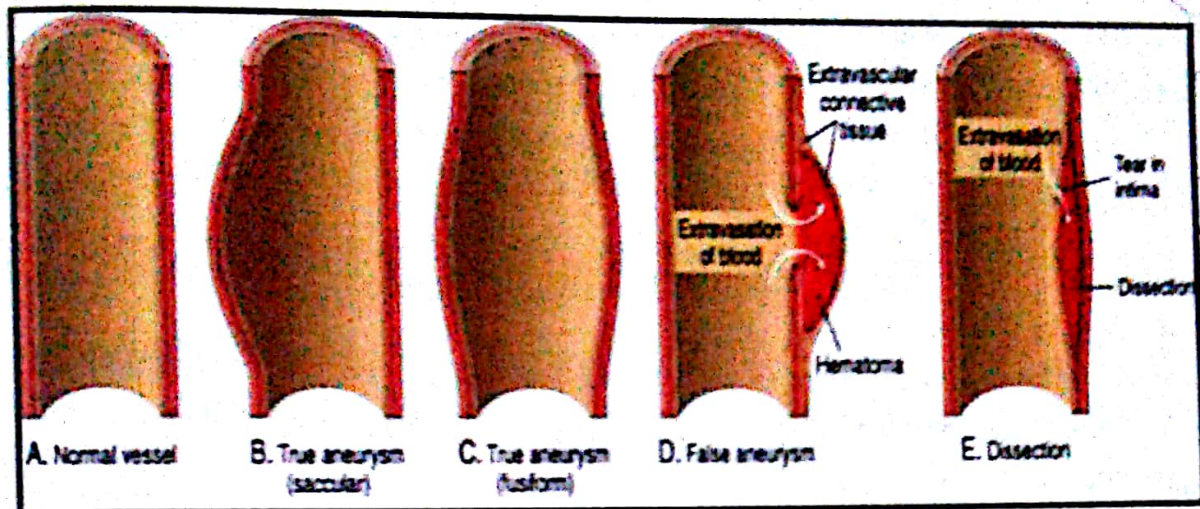


Fig. 1.8: A. Normal vessel. B. True aneurysm, saccular. C. True aneurysm, fusiform. D. False aneurysm. E. Aortic dissection.

Aortic dissection:

It occurs when the blood passes into the diseased media where it separates the wall into an inner layer (intima and part of media) and an outer layer (part of the media and adventitia).

Causes:

- 1- Myxomatous degeneration of the media due to genetic factors with rupture of unsupported vasa vasora (intramural haemorrhage).
- 2- Hypoxic medial damage consequent to narrowing of vasa vasorum by hypertensive changes.

Effects:

The false lumen may rupture internally to recommunicate with the true lumen or externally and depending on the site of rupture results in:

- 1- Haemopericardium with cardiac tamponade.
- 2- Mediastinal haemorrhage.
- 3- Haemothorax.
- 4- Abdominal haemorrhage.

Raynaud Phenomenon

A condition resulting in paroxysmal pallor or cyanosis of the fingers with/or toes, infrequently the nose, ear lobes, or lips when a person is exposed to cold or emotional stress.

- 1- Primary Raynaud phenomenon: It results from an exaggerated vasoconstriction of digital arteries and arterioles.
- 2- Secondary Raynaud phenomenon: Refers to vascular insufficiency of the extremities due to arterial disease as in SLE, scleroderma, Buerger's disease, or even atherosclerosis.

Diseases of Veins

Varicose veins:

They are dilated, elongated and tortuous veins.

Incidence: More common in females.

Sites: a- In systemic veins: usually in the leg veins.

b- In portal veins: sites of porto-systemic anastomosis.

Causes:

1. Deficient support of the venous wall (age).
2. High pressure within the lumen (e.g. prolonged standing, portal hypertension).

Complications:

- (1) Oedema.
- (2) Thrombosis.
- (3) Embolism.
- (4) Haemorrhage.
- (5) Infection i.e. thrombophlebitis.
- (6) Trophic skin changes (e.g. varicose ulcers).

Venous thrombosis: (see chapter of hemodynamic disorders)

a- Phlebothrombosis:

It is thrombosis of non-inflammatory origin.

b- Thrombophlebitis:

It is thrombosis initiated by inflammation.

Superior and inferior vena caval syndromes:

The superior vena caval syndrome:

Causes: Neoplasms that compress or invade the superior vena cava (e.g., bronchogenic carcinoma or mediastinal lymphoma).

Effects: The resulting obstruction produces;

- Marked dilation of the veins of the head, neck, arms with cyanosis.
- Respiratory distress due to compression of pulmonary vessels.

The inferior vena caval syndrome can be caused by neoplasms that compress or invade the inferior vena cava (IVC) or by a thrombus from the hepatic, renal or lower extremity veins that propagates upward.

Effects: IVC obstruction induces:

- ☐ Marked lower extremity edema, distention of the superficial collateral veins of the lower abdomen.
- ☐ Renal vein involvement produces massive proteinuria.

Diseases of the lymphatic vessels

Lymphangitis:

It is an acute inflammation of lymph vessels elicited by bacterial infection.

Morphology: The affected lymphatics are dilated and filled with an inflammatory exudate which may extend into the perilymphatic tissues.

Clinical:

- ♦ Red, painful subcutaneous streaks (the inflamed lymphatics).
- ♦ Painful enlargement of the draining lymph nodes (acute lymphadenitis).

Lymphedema:

Causes:

- 1- **Primary:** congenital lymphedema, resulting from lymphatic agenesis or hypoplasia.
- 2- **Secondary** or obstructive lymphedema as in;
 - a- Malignant tumors obstructing either the lymphatic channels or the regional lymph nodes.
 - b- Surgical procedures that remove regional groups of lymph nodes.
 - c- Post-irradiation fibrosis.
 - d- Filariasis.
 - e- Post-inflammatory thrombosis and scarring.

Regardless of the cause, lymphedema increases the hydrostatic pressure in the lymphatics behind the obstruction and causes increased interstitial fluid.

- Effects:**
- 1- Persistence of this edema leads to increased deposition of interstitial connective tissue, with tissue expansion, brawny induration or peau d'orange appearance of the overlying skin.
 - 2- Skin ulcers due to inadequate tissue perfusion.

NB: Milky accumulations of lymph in various spaces are designated chylous ascites (abdomen), chylothorax, and chylopericardium; these are caused by rupture of dilated lymphatics, typically obstructed secondary to an infiltrating tumor mass.

Tumours of blood vessels

Benign tumours: see chapter of neoplasia

- *Capillary and cavernous haemangiomas.*
- *Glomus tumor (Glomangioma):* It is a benign, painful tumor arising from glomus bodies (involved in thermoregulation). They usually occur under the fingernails.

Malignant tumours:

- *Angiosarcoma.*
 - It most often occurs in the skin, soft tissue, breast, and liver.
 - Hepatic angiosarcomas are associated arsenical pesticides, Thorotrast and polyvinyl chloride.

- *Kaposi sarcoma (KS):*

It is caused by Kaposi sarcoma herpesvirus (human herpesvirus-8).

Four forms of KS are recognized:

- a- *Classic KS:* affects European and Mediterranean older men.
It manifests as skin lesions usually on the distal lower extremities.
 - b- *Endemic African KS:* occurs in younger persons and frequently involves lymph nodes
 - c- *AIDS-associated KS:* is now the most common tumor in central Africa.
A severe form, with prominent lymph node and visceral involvement. It occurs in prepubertal children.
 - d- *Transplantation-associated KS:* occurs in patients on immunosuppression for organ transplant. It involves lymph nodes, mucosa, and viscera. Lesions often regress with reduction of immunosuppression.
- Gross:** Cutaneous lesions appear as multiple red-purple patches, plaques or nodules that may disseminate.
- Microscopic:** There is spindle shaped endothelial cells with slit-like vascular spaces and extravasated RBCs.

Diseases of the Heart

Congenital Heart Diseases:

Congenital heart diseases are abnormalities of the heart or great vessels that are present at birth.

Pathogenesis:

The development of the heart from a single tube occurs in the 5th to 8th week intra-uterine life.

The real cause is unknown but some factors are included such as:

- (1) Viral infections of pregnant mother during the first three months of gestation by: a- Rubella b- Cocksackie or other viruses.
- (2) Teratogens; as thalidomide, ...
- (3) Recessive inheritance factor, most common in association with chromosomal abnormalities (e.g., trisomies 13, 15, 18, and 21 and Turner's syndrome)
- (4) Maternal diabetes

Classification:

I- Acyanotic group (Left to right shunt);

- a- Atrial septal defects (ASDs).
- b- Ventricular septal defects (VSDs) and patent ductus arteriosus (PDAs).

II. Cyanotic group (Right to left shunt);

- (1) Fallot's tetralogy.
- (2) Transposition of great vessels.

III. Coarctation of the aorta (no shunt);

Atrial septal defect:

- This is one of the commonest congenital malformations of the heart.
- The foramen ovale may remain patent (Fig. 1.9).
- With a large atrial septal defect, blood flows from left to right atrium.
- Both right atrium and right ventricle become dilated and hypertrophied.
- The right ventricle fails, then congestive heart failure develops.

Ventricular septal defect:

Only 20% to 30% of VSDs occur in isolation; most are associated with other cardiac malformations (Fig. 1.10).

Effects:

- 1- Small VSDs may be asymptomatic
- 2- Larger VSD, result in:
 - ❑ Chronic severe left-to-right shunting, often complicated by pulmonary hypertension and congestive heart failure.
 - ❑ Progressive pulmonary hypertension, with resultant reversal of the shunt and cyanosis occurs earlier and more frequently than with ASDs.

Patent ductus arteriosus:

- ♦ During intrauterine life, the blood passes from the pulmonary artery through the ductus arteriosus into the aorta bypassing the oxygenated lungs (Fig. 1.11).
- ♦ Shortly after birth, this ductus is usually constricted in response to increased arterial oxygenation, decreased pulmonary vascular resistance and declining local levels of prostaglandin E₂.
- ♦ PDA becomes obliterated by about the 8th week after birth.

Effects of PDA:

- 1- A small PDA generally causes no symptoms.
- 2- Larger PDA can lead to cyanosis and congestive heart failure.

Fallot's tetralogy:

It is the most common cause of cyanotic congenital heart disease and accounts for about 5% of all congenital cardiac malformations.

It is a common lesion which shows the following four abnormalities:

- a- Ventricular septal defect.
- b- Overriding of the VSD by the aorta.
- c- Pulmonary stenosis.
- d- Hypertrophy of the right ventricle (Fig. 1.12).

Effects:

- Right-to-left shunting, decreased pulmonary blood flow, and increased aortic blood volume.
- The clinical severity depends on the degree of the pulmonary stenosis.
- Secondary polycythemia and clubbing of fingers due to hypoxia.
- Also increases the risk for infective endocarditis and systemic embolization.

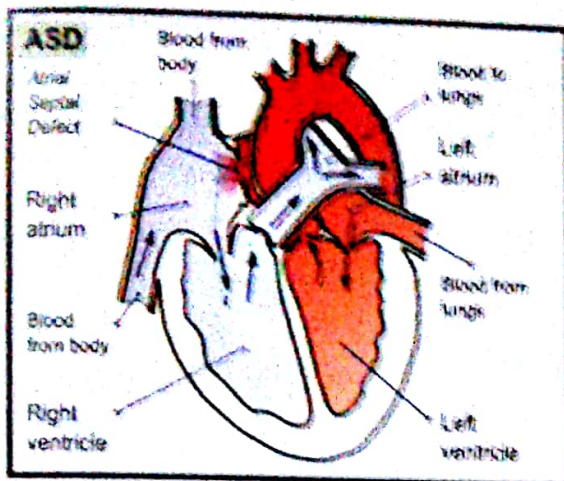


Fig.1.9: Atrial septal defect.

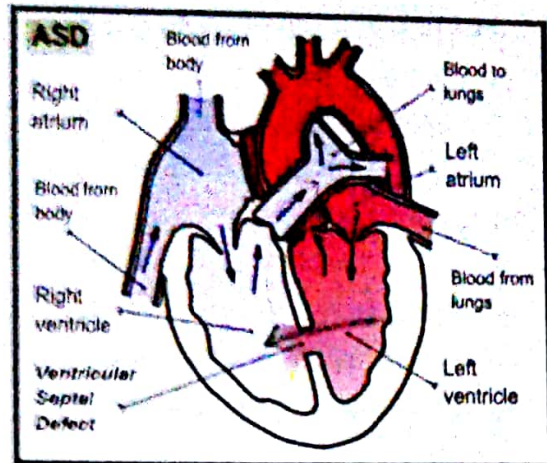


Fig.1.10: Ventricular septal defect

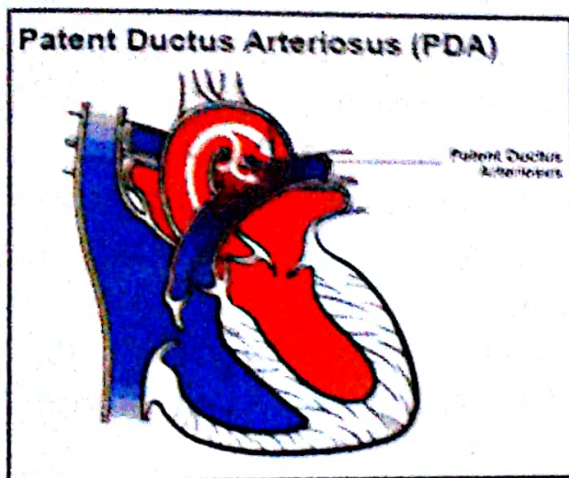


Fig.1.11: Patent ductus arteriosus

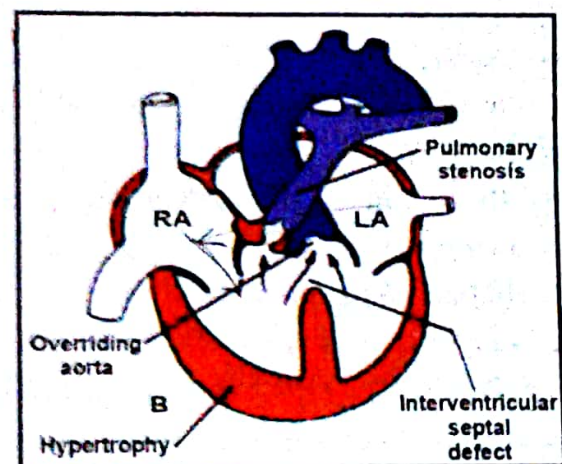


Fig.1.12: Tetralogy of Fallot.

Transposition of great vessels:

- This anomaly results from failure of the proximal aorta and pulmonary artery to undergo the rotation necessary for the establishment of their correct relationship with the ventricles.
- In consequence the aorta arises from the right ventricle and the pulmonary artery from the left (Fig.1.15).
- In this condition, the chief difficulty is with the effectiveness of the mechanism allowing oxygenated blood to reach the systemic circulation.

Coarctation of the aorta:

It means narrowing or constriction of the aorta.

- (a) Infantile (preductal) type: In which the narrowing of the aorta occurs proximal to the ductus arteriosus which remains patent, through which the blood flows from the pulmonary artery to the aorta. It is fatal.

(b) **The adult (postductal) type** In which the narrowing of the aorta occurs distal to the ductus arteriosus, which is usually closed.

Clinical: Increased pressure in the arm, head and neck, with decrease pulse and blood pressure in the legs.

Complications of congenital heart diseases:

- 1- Cyanosis: develops early in life in Fallot's tetralogy.
- 2- Predisposition to subacute infective endocarditis.
- 3- Heart failure unless corrected by operation.
- 4- Pulmonary hypertension.

Ischaemic heart diseases (IHD)

IHD are disorders of the heart resulting from an imbalance between cardiac blood supply (perfusion) and myocardial oxygen demand.

Causes:

(a) **Reduction of coronary blood flow** is the most important factor. It may be caused by:

- (1) Atherosclerosis (98%).
- (2) Occlusive coronary thrombosis.
- (3) Coronary embolism from the aortic valve.
- (4) Coronary spasm.
- (5) Dissecting aneurysm.
- (6) Polyarteritis nodosa.
- (7) Syphilitic aortic stenosis and syphilitic aortic incompetence.
- (8) Calcific aortic stenosis.
- (9) Diminished blood volume (e.g., with hypotension or shock).

(b) **Increased myocardial demands for oxygen**

- (1) Severe exercise and increased heart rate.
- (2) Hypertension (due to myocardial hypertrophy).
- (3) Valvular diseases.
- (4) Coarctation of the aorta which leads to left ventricular hypertrophy.

(c) **Decreased oxygen-carrying capacity of blood** (e.g., anaemia, carbon monoxide poisoning and diminished oxygenation (e.g., pneumonia, CHF))

Any of the aetiological factors mentioned above may lead to:

- I- Angina pectoris (stable or unstable)
- II- Chronic ischaemic heart disease (IHD) with CHF.
- III- Myocardial infarction (MI).
- IV- Sudden cardiac death (S.C.D.)

I- **Angina pectoris:**

It is an intermittent chest pain caused by transient, reversible myocardial ischemia.

Anginal pain is probably a consequence of the ischemia-induced release of adenosine, bradykinin and other molecules that stimulate the autonomic afferents. Three variants are recognized:

1- **Typical or stable angina:**

- It is precipitated by exertion, emotional stress or exercise and is relieved by rest or sublingual nitroglycerine.
- Pain is classically described as a crushing or squeezing substernal sensation that radiate down the left arm or to the left jaw (referred pain).

2- **Prinzmetal angina:**

- It occurs at rest and is caused by coronary artery spasm. Although such spasms typically occur on or near existing atherosclerotic plaques, completely normal vessel can be affected.
- Prinzmetal angina typically responds promptly to vasodilators such as nitroglycerin and calcium channel blockers.

3- **Unstable angina (also called crescendo angina):**

- It is characterized by increasingly frequent pain, precipitated by less exertion or even occurring at rest. It is preinfarction angina.
- It is associated with plaque disruption and superimposed thrombosis, distal embolization of the thrombus, and/or vasospasm.

II- **Chronic ischemic heart disease:**

It is a progressive heart failure secondary to ischemic myocardial damage. In most instances, there is a history of previous MI.

It is a disease of late decades of life.

Gross: Left ventricular dilation and hypertrophy, discrete areas of gray-white scarring from previous healed infarcts. There is moderate to severe atherosclerosis of the coronary arteries, sometimes with total occlusion.

Microscopic: Include myocardial hypertrophy, diffuse subendocardial myocyte vacuolization, and fibrosis from previous infarction.

III- **Myocardial Infarction:**

It is also commonly referred to as "heart attack".

Definition: It is necrosis of heart muscles resulting from ischemia.

- It is common in males between 45-54 years.
- It is 4-5 times common in males as in females; risk becomes equal in both sexes at 70 years.
- Risk factors as atherosclerosis.

Pathogenesis:

- ◆ MI is due to sudden thrombotic occlusion of atherosclerotic stenosed coronaries by atherosclerosis (*Fig.1.13*).
- ◆ Vasospasm and platelet aggregation can contribute.
- ◆ **MI especially subendocardial type** may occur without thrombotic occlusion as follows:
 - a- A stenosed artery with excessive exertion leads to increased heart rate and decreased O_2 flow with consequent MI without thrombosis.
 - b- During night, slow heart rate leads to diminished coronary perfusion followed by MI in already stenosed coronaries.

NB:

- Angiography performed within 4 hours of the onset of MI demonstrates coronary thrombosis in 90% of cases. While, 12 to 24 hours after onset of symptoms, evidence of thrombosis is seen in only 60% of patients, even without intervention.
- Thus, at least some occlusions clear spontaneously through lysis of the thrombus or relaxation of spasm.
- This sequence of events in a typical MI also has therapeutic implications: *Early thrombolysis by streptokinase or tissue plasminogen activator and/or angioplasty can be highly successful in limiting the extent of myocardial necrosis.*

Gross and microscopic appearances of MI are tabulated in table 2.

Table (2): Morphologic changes in myocardial infarction (Irreversible)

Elapse d time	Gross changes (Fig.1.15,17)	Light microscopy (Fig.1.14,16,18)
0.5-2 hours	None	Usually none, variable waviness of fibers at border
4-12 hours	Occasionally dark mottling	Beginning coagulative necrosis, edema hemorrhage
12-24 hours	Dark mottling	Ongoing coagulative necrosis; cytoplasmic eosinophilia, nuclear pyknosis, marginal contraction band necrosis, beginning neutrophilic infiltrate.
1 - 3 Days	Pallor and mottling with yellow-tan infarct center	- Coagulative necrosis with loss of nuclei & striations & interstitial neutrophilic infiltrate.
3-7 Days	Hyperemic border, central yellow-tan softening.	-Beginning of disintegration of dead myofibers with dying neutrophil; early phagocytosis of dead cells by macrophages at infarct border.
7-10 days	Maximally yellow tan soft, with depressed red-tan margins	Well-developed phagocytosis of dead cells; early formation of fibrovascular granulation tissue at margins
10-14 days	Red-gray depressed infarct borders	-Well-established granulation tissue with new blood vessels and collagen deposition
2 - 8 Weeks	Gray white scar progressive from border toward core of infarct (Fig.1.21)	Increased collagen deposition, with decreased cellularity
>2 months	Scarring complete	Dense collagenous scar

NB: Reversible morphologic changes in MI occurs during 1½ hours, with no gross or microscopic changes only EM changes in the form of relaxation of myofibrils, glycogen loss and mitochondrial swelling.



Fig.1.13: Coronary artery with luminal thrombosis.

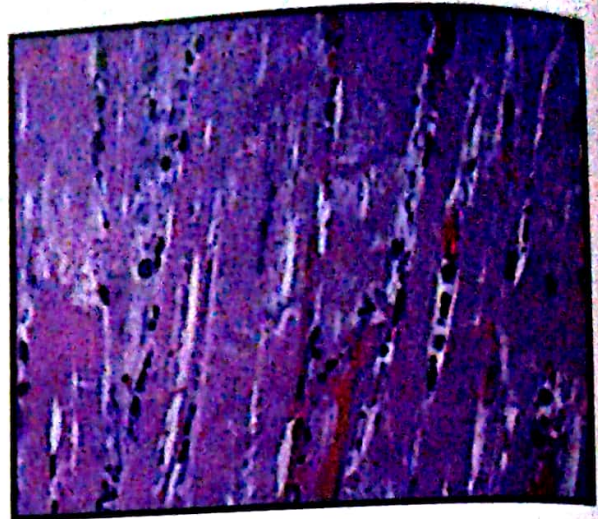


Fig.1.14: MI, the myocardial fibers lose cross striations & nuclei are not clearly visible.

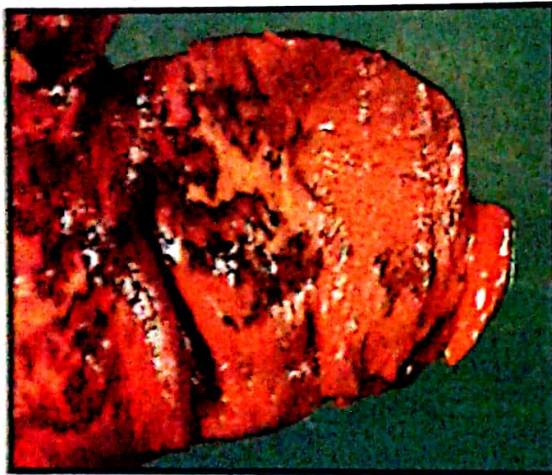


Fig.1.15: Left ventricular wall with a large recent MI

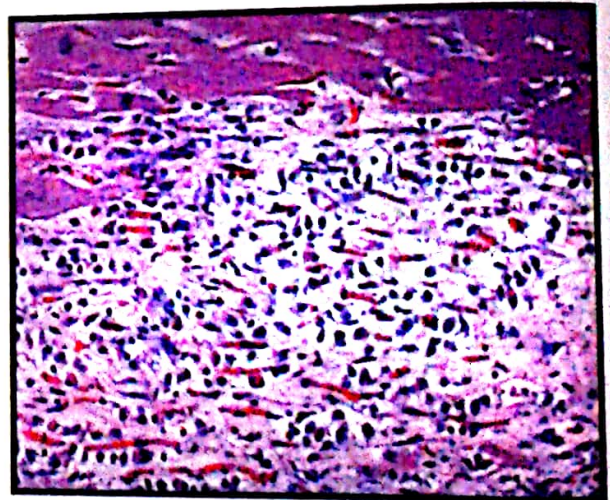


Fig.1.16: MI of 1 to 2 weeks. Few capillaries, macrophages & collagen



Fig.1.17: Transmural infarction of left ventricle with an aneurysm

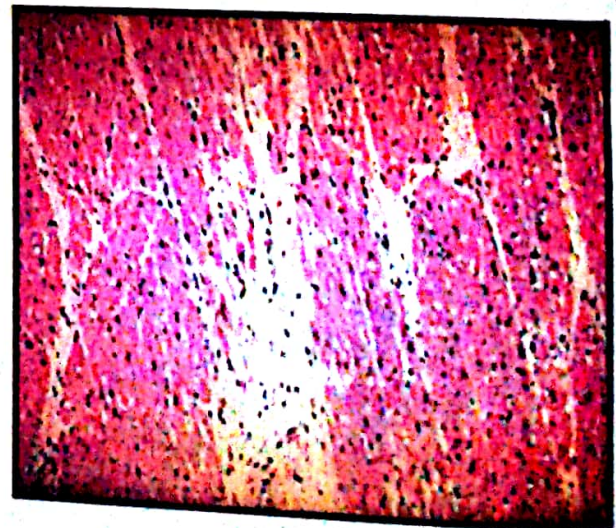


Fig.1.18: Healed infarction.

Myocardial response to ischemia:

Loss of the myocardial blood supply leads to profound functional, biochemical, and morphologic consequences as:

- A drop in ATP and accumulation of potentially noxious metabolites (e.g., lactic acid) in cardiac myocytes
- Necrotic myocardial cells release enzymes which are helpful in diagnosing MI:
 - Creatine kinase (CK) and specific cardiac isoform (CK-MB)
 - Lactate dehydrogenase (LDH)
 - Myocardial protein Troponin I (c-TnI)
- A rapid loss of contractility, which occurs within a minute of the onset of ischemia
- It also contributes to arrhythmias, probably by causing **electrical instability (irritability)** of ischemic regions of the heart.
- Only severe ischemia lasting 20 to 40 minutes causes irreversible injury and myocyte death. MI reaches its full size in 3 to 6 hours; intervention during this time can limit the final extent of necrosis.

Frequency of coronary artery involvement and resultant area in transmural infarction (Sites):

- 1- Acute occlusion of the proximal left anterior descending (40-50%)
Resultant area is the anterior wall of the left ventricle, apex and the anterior 2/3 of the interventricular septum.
- 2- Acute occlusion of right coronary (30 - 40%): affects much of the right ventricle, the posterior wall of the left ventricle and the posterior 1/3 of the interventricular septum.
- 3- Acute occlusion of the proximal left circumflex (15- 20%): will cause necrosis of the lateral left ventricle.

Size and rate of development of an acute MI depend on:

- 1- The size and distribution of the involved vessel.
- 2- The rate of development and the duration of the occlusion.
- 3- Metabolic demands of the myocardium (affected, for example, by blood pressure and heart rate).
- 4- Extent of collateral supply.

Patterns of myocardial infarction (Fig.1.19):

- (1) **Subendocardial Infarctions:** This is a multifocal nonconfluent area of necrosis, extending from the subendocardium to involve 1/3 to 1/2 of thickness of the left ventricle. It is not accompanied by thrombosis in 90%, but by arrhythmias thus, being dangerous.

- (2) Transmural infarctions: involve the full thickness of the ventricle and are caused by epicardial vessel occlusion through a combination of chronic atherosclerosis and acute thrombosis
- (3) Microscopic infarcts: occur in the setting of small vessel occlusions. These can occur in cases of vasculitis, embolization of valve vegetations or mural thrombi, or vessel spasm due to elevated catecholamines either endogenous (e.g., pheochromocytoma or extreme stress), or exogenous (e.g., cocaine)

Complications of transmural infarction:

1. Arrhythmia.
2. Acute left ventricular failure and sudden death.
3. Rupture of papillary muscle, ventricle and perforation of the interventricular septum leading to acute left ventricular failure, cardiac tamponade and left to right shunt.
4. Mural thrombosis resulting in embolisation.
5. Fibrosis leading to aneurysmal dilatation and embolisation.
6. Pericarditis which may be fibrinous or hemorrhagic.
7. Congestive heart failure (CHF).

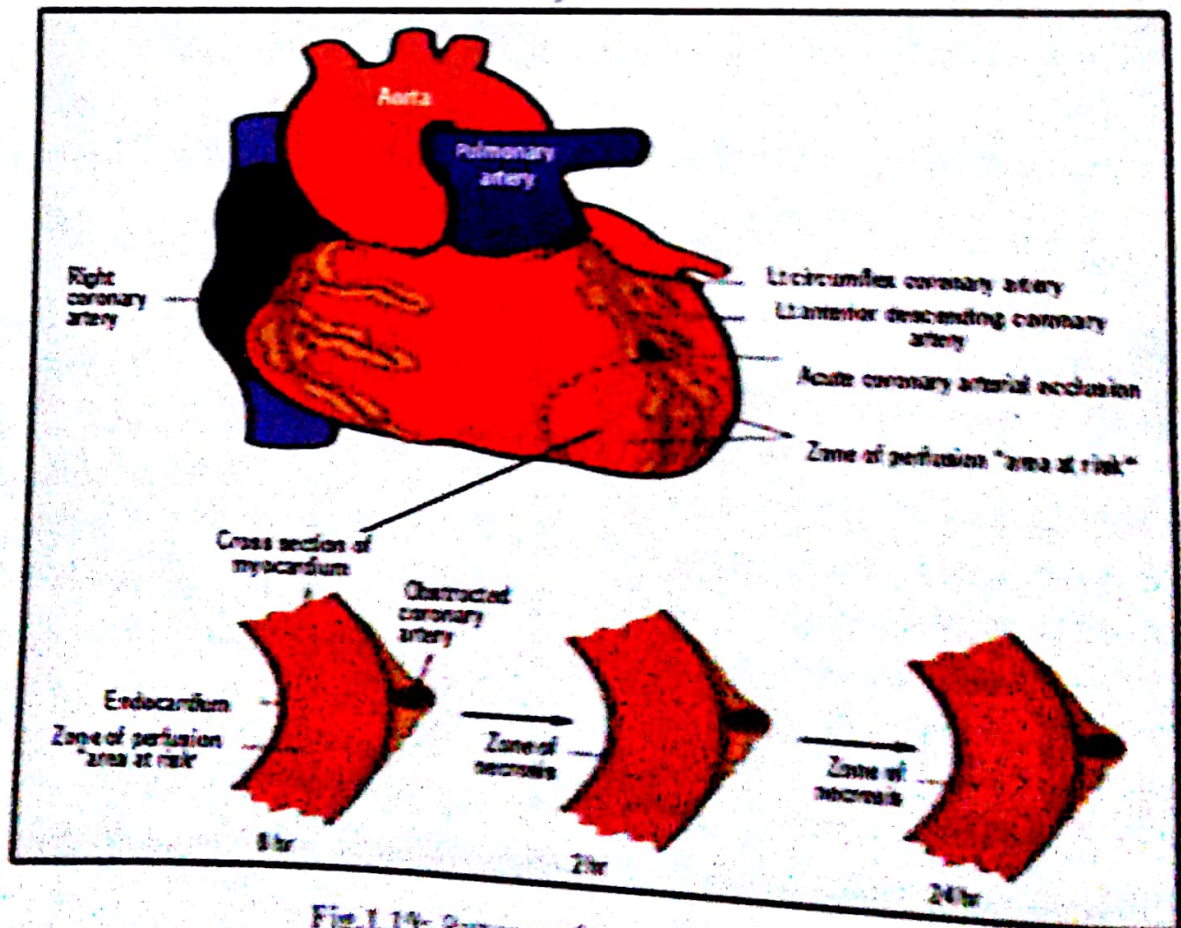


Fig.1.19: Patterns of myocardial infarction.

Hypertensive Heart Diseases:

1- Systemic hypertensive heart disease:

- Sustained systemic hypertension produces hypertrophy of the left ventricle. The heart weight can exceed 500 g (normal, 320 to 360 g) and the left ventricular wall thickness can exceed 2 cm (normal 1.2 to 1.4 cm).
- When the cardiac reserve is exhausted, the ventricle will dilate and congestive heart failure appears.
- Hypertension is commonly associated with coronary atherosclerosis, depriving the thickened myocardium of the essential oxygen and myocardial infarction is a common complication.

2- Pulmonary hypertensive heart disease (Cor-Pulmonale):

Cor-pulmonale consists of right ventricular hypertrophy and dilation frequently accompanied by right heart failure caused by pulmonary hypertension attributable to primary disorders of the lung parenchyma or pulmonary vasculature.

Types:

- 1- Acute cor-pulmonale follows massive pulmonary embolism.
- 2- Chronic cor-pulmonale occurs secondary to prolonged pressure overloads in chronic lung and pulmonary vascular diseases.
 - The right ventricle and atrium often are dilated.
 - The pulmonary arteries often contain atheromatous plaques.

Degeneration and infiltration of the heart

(1) Brown atrophy: It is frequently associated with wasting diseases and old age. The heart is small; the surface is wrinkled with loss of epicardial fat and tortuous coronaries. The muscles are brown coloured and friable.

(2) Cloudy swelling: It is associated with infections and many toxic states e.g. typhoid, influenza or septicaemia. The heart is soft, pale and with friable myocardium.

(3) Fatty heart:

- In obesity due to increased epicardial fat (fatty infiltration).
- Fatty change with accumulation of fat in myocardial fibers.

(4) Amyloidosis: Mostly seen in primary amyloidosis. The heart is firm, waxy with thickening of myocardium.

(5) Glycogen infiltration: In Von Gierke's disease (Glycogen storage disease), glycogen accumulates in the myocardial fibres with enlargement of the heart and disturbance of function.

Rheumatic Fever

Definition: It is an acute immunologically mediated multisystem inflammatory disease that occurs after infection with group A β -hemolytic streptococci (usually pharyngitis, but also rarely with infections at other sites such as skin).

Pathogenesis

- The disease occurs after a latent period of two to three weeks following an infection with group A β -hemolytic streptococci.
- An M protein, present on the surface of specific strains of streptococci, evoked the production of antibodies that are cross-reactive with human cardiac muscle and valve components, i.e. streptococcal antigen is immunologically closely related to the heart muscle and valve components.
- Cardiac injury occurs through the activation of complement and Fc receptor-bearing cells (including macrophages). CD4⁺ T cells that recognize streptococcal antigen also can cross-react with host antigens and elicit cytokine-mediated inflammatory responses (Fig.1.20).

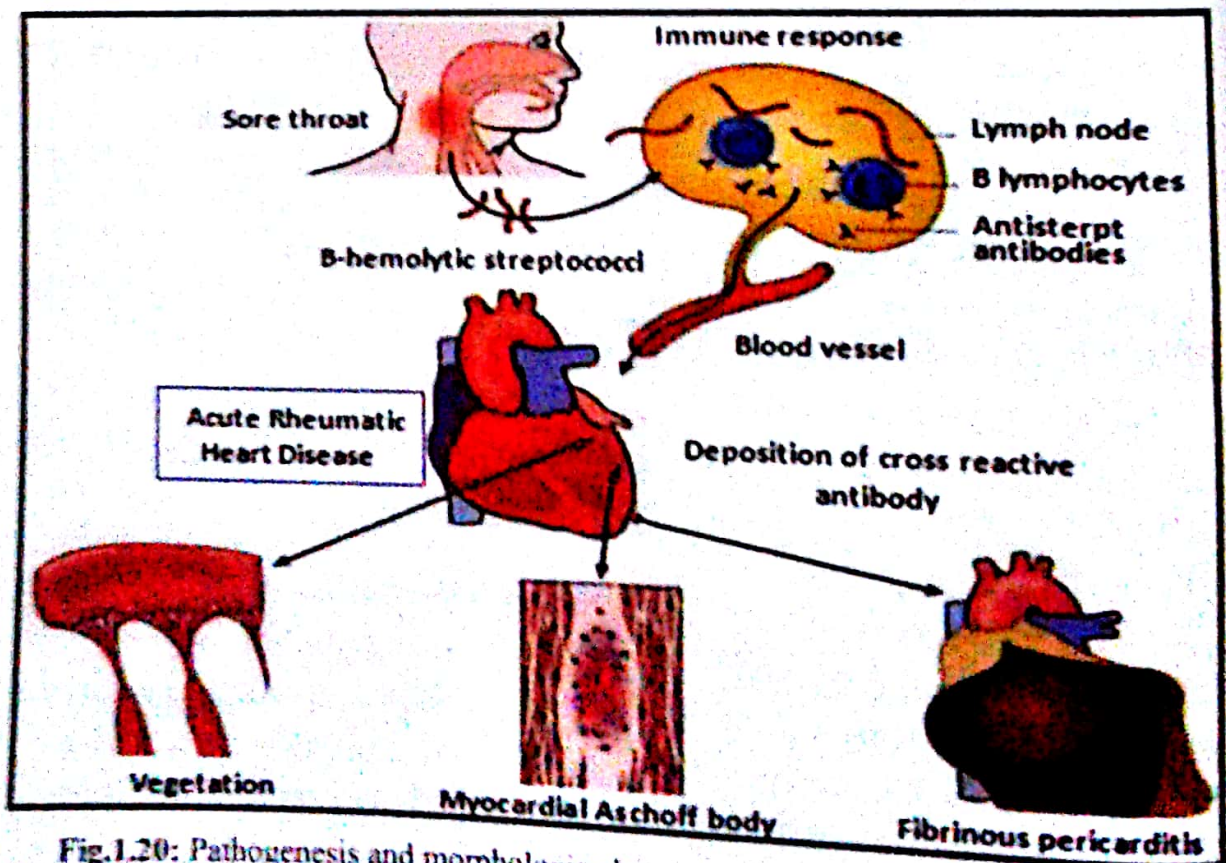


Fig.1.20: Pathogenesis and morphologic changes of acute rheumatic heart disease

Predisposing Factors:

- Age: 5 - 15 years and very rare in middle age.
- Sex: equal incidence.
- Tonsillitis or pharyngitis by group A B - hemolytic streptococci.
- Familial tendency due to genetic factors.
- Socioeconomic factors: i.e. overcrowding and damp areas.

Clinical manifestations:

- Fever, arthralgia, ECG changes, raised E.S.R. and leucocytosis.
- Elevated antistreptolysin O titre and C reactive protein in blood.

NB: Rheumatic fever licks the joints but bites the heart. Although the joints are the most frequent site affected, the involvement is reversible but the heart suffers the most disabling often irreversible damage.

A- Cardiac lesions of rheumatic fever:

Acute rheumatic fever affects the three cardiac layers of the heart, pericardium, myocardium and endocardium, i.e. "pancarditis".

- (1) **Pericarditis:** It is either serofibrinous, or serous inflammation with fibrin threads on both pericardial layers giving a "bread and butter" appearance on separating the two pericardial layers (Fig.1.21).

Fate: Generally resolves without sequelae or rarely fibrosis occurs with adhesions which may be diffuse or localized (Milk spots).

- (2) **Myocarditis:** It takes the form of scattered **Aschoff bodies**, which are pathognomonic for rheumatic fever. They can be found in the pericardium, myocardium, or endocardium (including valves).

Gross: The heart is enlarged, flabby with scattered pin head sized pale greyish foci which appear after four weeks.

Microscopic: Aschoff bodies are seen within the interstitial connective tissue between the muscle fibres and in relation to intramyocardial blood vessels (Fig1.22).

Aschoff bodies; are formed of central fibrinoid necrosis, surrounded by lymphocytes, plasma cells, **Anitschkow cells** or **caterpillar cells** which are activated macrophages, the chromatin is disposed in the center of the nucleus in the form of a slender ribbon that resemble an attenuated body with innumerable finger-like projections (Fig.1.23) and **Aschoff multinucleated giant cells** which are fused activated macrophages.

1.1. Endocarditis:

- 1. Inflammation of the endocardium lining the cardiac chambers (mainly endocardium), especially that of left atrium, which is swollen, oedematous and red. Erosion by the flowing blood will lead to thrombosis. A focus of rough wrinkled endocardium in the posterior aspect of the left atrium, referred to as (Mac Callum's patch) denotes previous rheumatic involvement.
- 2. Inflammation of valvular endocardium.

1.2. Acute rheumatic valvulitis:

- 1. The valves are swollen, congested and oedematous, specially the mitral and aortic valves (70 - 75%) which are more subjected to pressure and more susceptible to damage than the tricuspid and pulmonary valves.
- 2. This condition is complicated by endothelial damage followed by platelet and fibrin thrombi called **rheumatic vegetations**.

Rheumatic vegetations:

Grains: They are multiple beaded thrombi (platelet and fibrin), which occur along the line of closure 2 - 3 mm from the free margin of the valve, firmly adherent to the atrial surface of mitral valve or ventricular surface of aortic valve. The thrombi are pale, pin head size and never give emboli (**Fig.1.20**)

Microscopic: They are **aseptic** and formed of platelets and fibrin on the valves with lymphocytes, plasma cells and Aschoff giant cells in the subendocardium.

1.3. Chronic rheumatic heart disease:

- 1. It is characterized by organization of the acute inflammation and subsequent scarring.
- 2. Aschoff bodies are replaced by fibrous scar and they are rarely seen.
- 3. Valve cusps and leaflets become permanently thickened and retracted.
- 4. The mitral valves exhibit leaflet thickening with intercommissural adhesions leading to marked **stenosis** with **fish mouth** or **button hole** appearance (**Fig.1.24**).
- 5. The chordae tendineae become thickened, fused and shortened leading to constant traction on the valve and **funnel shape** appearance of the valve.

Extracardiac manifestations:

- 1. Joints and adjacent musculo-fascial tissues: Fleeting arthritis with effusion, muscle pain and weakness. It affects large joints e.g. knees, elbow, wrists and shoulders.

- (2) Serous membranes: pericardial and sometimes pleural effusion.
- (3) Skin rash known as erythema marginatum with central pale area and red margin.
- (4) Small subcutaneous palpable nodules may be present over the body prominences subjected to pressure, for example the tibial surface.
- (5) Central nervous system involvement may appear in the form of chorea. This is involuntary spasmodic muscular movements.

Complications:

1. Arrhythmias (particularly atrial fibrillation in the setting of mitral stenosis).
2. Acute heart failure.
3. Embolism (from the mural thrombus).
4. Infective endocarditis.
5. Congested lung and pulmonary hypertension.



Fig. 1.21: Fibrinous pericarditis "bread and butter appearance"

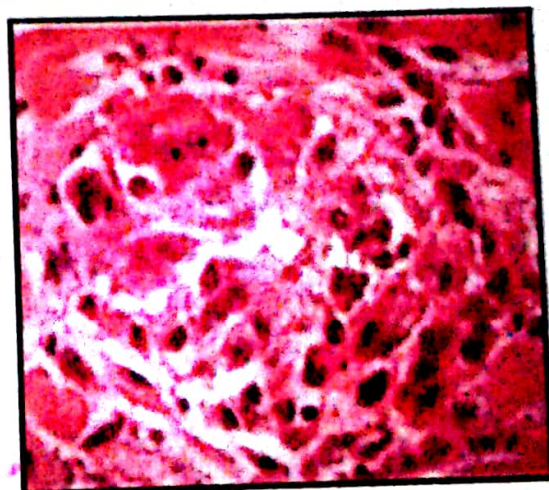


Fig. 1.22: Aschoff nodule

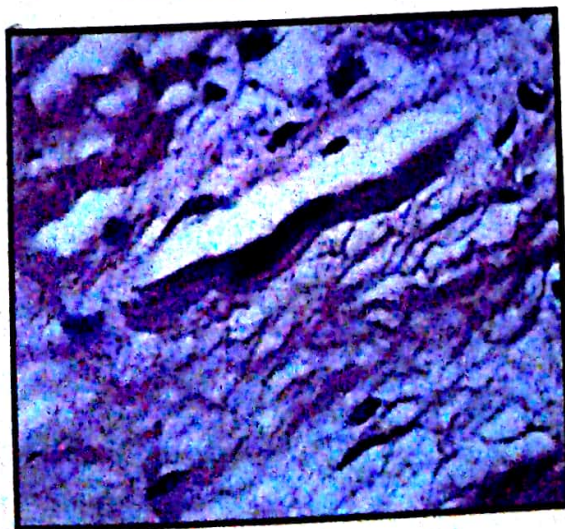


Fig. 1.23: Anitschkow cell



Fig. 1.24: Chronic rheumatic valvulitis mitral valve "fish mouth appearance"

Diseases of the endocardium

1- Endocarditis:

It means inflammation of the heart valves as well as the mural endocardium.

Types of endocarditis:

1. Rheumatic endocarditis (See page 34).
2. Infective endocarditis, which may be acute or subacute infective endocarditis.
3. Non-bacterial thrombotic endocarditis.
4. Atypical verrucous endocarditis.
5. Valvular lesions in carcinoid syndrome.

2- Infective endocarditis:

- It is characterized by colonization or invasion of the heart valves by microbiologic agent, thus leading to thrombotic masses laden with organisms, so called infective vegetation.
- It is subdivided clinically into acute and subacute forms based on the severity of the clinical course; that are attributable to the virulence of the responsible microbe and whether underlying cardiac disease is present or not.

Predisposing factors:

1. Congenital heart diseases most often ventricular septal defect and patent ductus arteriosus.
2. Small shunts or tight stenosis.
3. Chronic rheumatic valvulitis.
4. Mitral valve prolapse (myxomatous degeneration).
5. Degenerative calcific aortic valve stenosis.
6. Bicuspid valve (congenital anomaly).
7. Intra-venous drug abuse (especially the right side). e.g., drug addiction.
8. Artificial valves (prosthetic valve).

(a) Acute infective endocarditis:

It refers to destructive infections, frequently caused by a highly virulent organism attacking a previously normal valve, and capable of causing substantial morbidity and mortality even with appropriate antibiotic therapy and/or surgery.

Age: 50-60 years.

Causes:

- The commonest organism is staphylococcus aureus, less common is streptococci and pneumococci.
- Fungal endocarditis occurs after severe debilitating illness, after cardiac surgery, immunosuppressive steroid therapy or cancer therapy.

Gross: Bulky friable and destructive vegetations that occur commonly on mitral and aortic valves, causing ulceration, erosion and perforation of the valve and myocardium (*Fig.1.25*). The infected vegetations are easily detachable leading to embolic manifestations (septic infarcts).

Microscopic: It is an acute suppurative inflammation in the substance of the cusps. The vegetation is composed of tangled mass of fibrin, blood platelets, inflammatory cells and colonies of bacteria on ulcerated valve.

Fate and complications:

1. Local: Ulceration, perforation or rupture of the cusps and chordae tendeneae may occur.
2. General: Septic emboli forming distant septic infarcts, pyaemic abscesses (systemic pyaemia). Also toxemia or septicaemia may occur.

(b) Subacute infective endocarditis:

It refers to infections by organisms of low virulence involving a previously abnormal heart, especially scarred or deformed valves. Most of the patients survive with appropriate therapy.

Age: Young age and children.

Causes: Bacteremia of low virulent organism (e.g. Streptococcus viridans) following tooth extraction or tonsillitis. This organism is a normal inhabitant of the mouth and upper respiratory tract. It settles on a diseased valve (rheumatic valve or in congenital anomalies).

Gross: The vegetation is less bulky than the acute type, friable and easily detached. It is formed mainly on mitral and aortic valve and extending to adjacent endocardium (*Fig.1.26*).

Microscopic: The vegetations are composed of platelets, fibrin, polymorphs and colonies of bacteria. They often have granulation tissue at their bases (suggesting chronicity). Chronic inflammatory infiltrate, fibrosis, and calcification may develop over time.

Fate and complications:

- (1) The valvular lesions heal with scarring leading to deformity, so the preexisting rheumatic or congenital lesions become more severe.

(2) Embolic manifestations:

- i- Detached parts of the vegetations leading to aseptic infarcts due to the low virulence of organisms and the formation of antibodies. This may appear in spleen, kidneys and brain.
- ii- Mycotic aneurysm in the cerebral, superior mesenteric, renal and limb arteries due to lodgment of low grade infected emboli in the arterial wall via the vasa vasorum.

(3) Capillary lesions due to allergic vasculitis leading to:

- a- Skin lesions in the form of splinter haemorrhages or Osler's nodule (Fig. 1.27).
- b- Glomerulonephritis due to glomerular trapping of antigen-antibody complexes causing hematuria, albuminuria or renal failure
- c- Petechial haemorrhages in the skin, retina, conjunctiva, serous sacs and mucous membranes.

(4) General manifestations of toxæmia

Causes of death:

- Congestive heart failure.
- Embolic manifestations.
- Renal failure.
- Secondary bacterial infection due to lowered resistance

3- Non-bacterial thrombotic endocarditis: -

- They are sterile small vegetations (1 - 5 mm) formed of fibrin, platelets and blood elements on the line of valve closure. They are loosely attached to the valve.
- They usually arise on normal valve (mitral or aortic).
- Major complications are embolization and secondary infection.

Causes: They are due to hypercoagulable states as in;

- 1- Chronic disseminated intravascular coagulation; hyperestrogenic states, chronic sepsis and chronic debilitating illness (**Marantic endocarditis**).
- 2- Underlying malignancy, particularly mucinous adenocarcinomas. The latter association probably relates to the procoagulant effect of circulating mucin and/or tissue factor elaborated by these tumors.
- 3- Endocardial trauma, such as from an indwelling catheter.

Fate and complications:

1. Embolic manifestations leading to infarctions in brain, spleen, kidney, heart and intestine.

2. Bacterial colonization and the consequent development of infective endocarditis.



Fig. 1.25: Acute infective endocarditis; the aortic valve cusps are destroyed



Fig. 1.26: Subacute infective endocarditis; the valve demonstrates a large, irregular reddish vegetation



Fig. 1.27: Splinter hemorrhage; under the nail



Fig. 1.28: Calcification of aortic valve cusps

4- Atypical verrucous endocarditis (Libman-Sacks endocarditis):-

It occurs in cases of SLE, in the form of sterile small vegetations on both surfaces of the valve, namely mitral and tricuspid valves.

The lesions probably develop as a consequence of immune complex deposition and thus exhibit associated inflammation, often with fibrinoid necrosis of the valve substance adjacent to the vegetation with subsequent fibrosis and serious deformity.

5- Valvular lesions in carcinoid tumour and syndrome:-

- ♦ Right valve lesions occurs in carcinoid syndrome (Flushing, bronchoconstriction and diarrhea) due to circulation of 5-hydroxytryptamine released by intestinal carcinoid tumor with massive metastasis in the liver (escaping hepatic degradation).

- ♦ The left side of the heart is not affected as this vasoactive substance is probably destroyed in its passage through the lungs.

However, left-sided heart carcinoid lesions can occur in:

- Atrial or ventricular septal defects with right-to-left flow
- In association with primary pulmonary carcinoid tumors

Gross: Plaque like thickening of the tricuspid and pulmonary valves.

Microscopic: The lesions are composed of smooth muscle cells and sparse collagen fibers embedded in an acid mucopolysaccharide-rich matrix.

Valvular Heart Disease:

A- Degenerative valve disease:

It is a term used to describe changes that affect the integrity of valvular extracellular matrix (ECM). Degenerative changes in the cardiac valves probably are an inevitable part of the aging process.

1- Calcific Aortic Stenosis:

It is the most common cause of aortic stenosis.

The pathologic changes are fibrosis and calcification (**Fig. 1.28**).

Age incidence: In anatomically normal valves it manifests at the age of 70-80 years, while in bicuspid aortic valves at 40 to 50 years.

Pathogenesis: Chronic injury due to hyperlipidemia, hypertension, inflammation, and other factors implicated in atherosclerosis.

Clinically: The development of angina, CHF or syncope in aortic stenosis carries a poor prognosis.

2- Myxomatous mitral valve:

In myxomatous degeneration of the mitral valve, one or both mitral leaflets are "floppy" and prolapsed back into the left atrium during systole.

Incidence: Affects 0.5% to 2.4% of adults.

Pathogenesis:

- Primary myxomatous degeneration is of unknown etiology.
- Secondary myxomatous change may result from injury to the valve myofibroblasts, induced by chronically aberrant hemodynamic forces.

Gross:

- Ballooning of the mitral leaflets.
- The chordae tendineae tend to be elongated, thinned and may rupture.
- Concomitant tricuspid valve involvement is frequent (20- 40% of cases).

Microscopic:

- There is thinning of the **fibrosa** layer of the valve.
- Expansion of the middle **spongiosa** layer owing to increased deposition of myxomatous (mucoid) material.

Clinical: Most cases are asymptomatic

Complications: Occur in 3% of cases

- 1- Infective endocarditis
- 2- Sudden cardiac death due to ventricular arrhythmia.
- 3- Stroke or systemic infarction may rarely occur from embolism of thrombi formed in the left atrium.

Acquired heart valve diseases (Table. 1.2):

Table.1.2: Major causes and effects of acquired heart valve diseases.

<u>Valve</u>	<u>Causes</u>	<u>Effects</u>
<u>Mitral Stenosis</u>	- Chronic rheumatic valvulitis. - Infective endocarditis.	- a- Dilated left atrium in which thrombosis may occur. - b- The left ventricle is of normal size, unless mitral incompetence is present. - c- Right ventricular hypertrophy. - d- CVC of the lungs with pulmonary hypertension.
<u>Mitral Regurgitation</u>	- Chronic rheumatic valvulitis. - Infective endocarditis. - Rupture of papillary muscle or dysfunction. - Rupture of chordae tendineae.	- a- Dilated and hypertrophied left ventricle. - b- Dilated left atrium. - c- CVC of the lungs and pulmonary hypertension. - d- Right ventricular hypertrophy.
<u>Aortic Stenosis</u>	- Chronic rheumatic valvulitis. - Infective endocarditis. - Calcific aortic stenosis.	- a- Left ventricular hypertrophy. - b- Coronary artery insufficiency. - c- Cerebral vascular insufficiency with syncopal attacks. - d- Sudden death, due to ventricular fibrillation.
<u>Aortic Regurgitation</u>	- The same causes as for aortic stenosis. - Syphilitic aortitis. - Ankylosing spondylitis - Marfan syndrome	- a- Left ventricular dilatation - b- Left ventricular hypertrophy

Cardiomyopathies:

They are cardiac diseases attributable to intrinsic myocardial dysfunction.

They are divided into:

Primary, principally confined to the myocardium.

Secondary presenting as cardiac manifestation of a systemic disorder.

Types of cardiomyopathy (Fig. 1.29).

1- Hypertrophic cardiomyopathy (HCM):

It is characterized by myocardial hypertrophy, defective diastolic filling and in one third of cases ventricular outflow obstruction.

Pathogenesis:

- Most cases of HCM are caused by point mutations in one of the genes encoding proteins that form the contractile apparatus.
- In most cases, the pattern of transmission is autosomal dominant.

Gross: Massive asymmetrical hypertrophy of the left ventricle, especially of the interventricular septum but with no dilatation.

Microscopic:

- The left ventricle shows hypertrophy of myocytes and interstitial fibrosis (Fig. 1.30).
- There are areas of disarray in which there is a disordered whorly arrangement of muscle fibres and loss of normal cellular orientation.

Clinical:

- a- Decreased compliance of left ventricle which interferes with diastolic filling.
- b- The asymmetrical hypertrophy of the septum may obstruct the outflow from the left ventricle.
- c- Mitral regurgitation due to distortion of ventricle by asymmetrical hypertrophy.

2- Dilated cardiomyopathy (DCM):

It is characterized by progressive cardiac dilatation and contractile systolic dysfunction usually with concurrent hypertrophy.

Pathogenesis:

- Genetic causes: DCM has a hereditary basis in 20% to 50% of cases.
- Infection: Coxsackie virus B and other enteroviruses can occasionally be detected in the myocardium from late-stage DCM patients.

- Alcohol or other toxic exposure.
- Peripartum cardiomyopathy; occurs late in gestation or postpartum.
- Iron overload; in the heart can result from hereditary hemochromatosis.

Gross:

- All chambers are dilated.
- The myocardium is pale and flabby, ventricular mural thrombus and endocardial thickening are present.

Microscopic:

- Some myocardial fibres show hypertrophy while others appear thinned.
- There may be interstitial fibrosis with an increase of chronic inflammatory cells (*Fig. 1.31*).
- These patients present with unexplained congestive heart failure.

3- Restrictive cardiomyopathy (RCM):

It is characterized by a primary decrease in ventricular compliance resulting in impaired ventricular filling during diastole, the wall is stiff.

Pathogenesis:

- a- Idiopathic accounts for 10% of cases of childhood heart disease in tropical areas. Microscopic examination reveals variable degrees of interstitial fibrosis.
- b- Associated with systemic disease as in;
 - 1- **Amyloidosis**; deposition of amyloid material in systemic amyloidosis or can be restricted to the heart in *senile cardiac amyloidosis*.
 - 2- **Endomyocardial fibrosis**:
It is a disease of children and young adults in Africa and other tropical areas; characterized by dense diffuse fibrosis of the ventricular endocardium and subendocardium.
It is linked to nutritional deficiencies and/or inflammation related to helminthic infections (e.g., hypereosinophilia).
Worldwide, it is the most common form of RCM.
 - 3- **Loeffler endomyocarditis**:
Characterized by endocardial fibrosis, associated with large mural thrombi, peripheral eosinophilia and eosinophilic tissue infiltrates.
Release of eosinophil major basic protein, results in endo and myocardial necrosis, followed by scarring of the endocardium and thrombosis.

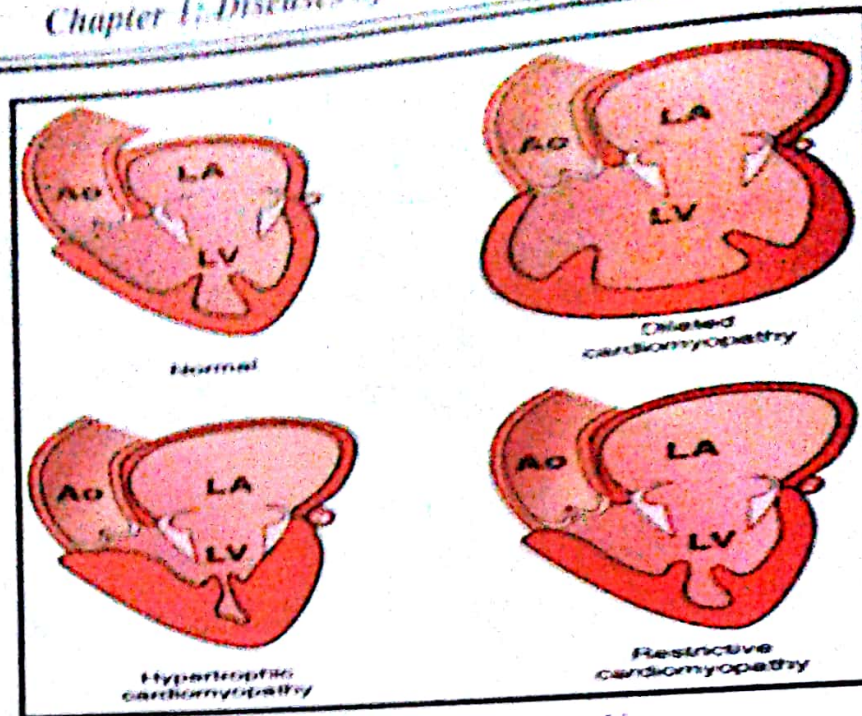


Fig. 1.29: Types of cardiomyopathies

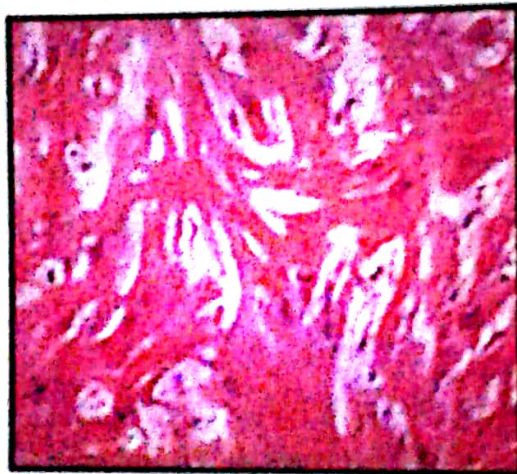


Fig. 1.30: HCM, hypertrophied muscle fibres

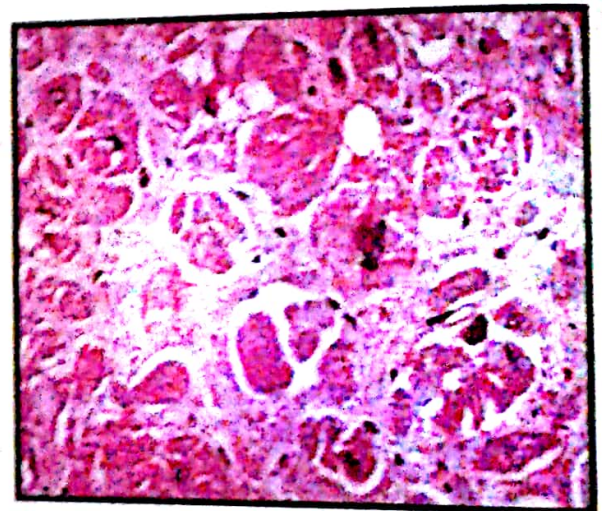


Fig. 1.31: DCM; variable myocyte hypertrophy & interstitial fibrosis.

Myocarditis:

It is myocardial damage caused by inflammatory infiltrates secondary to infections or immune reactions.

Coxsackie viruses A and B are the most common pathogens in the United States.

Clinical; Myocarditis can be asymptomatic. It may give rise to acute heart failure, or evolve to DCM.

Types of myocarditis:

(1) Suppurative myocarditis (rare).

Causes: Suppurative organisms, such as streptococci...etc., which reach the myocardium via:

1. Blood: as in septicaemia and pyaemia.
2. Direct extension: as a complication of suppurative endocarditis, suppurative pericarditis and suppuration of the lung and pleura.

Microscopic: There is focal acute suppurative inflammation of the interstitial tissues with destruction of the muscle fibres and even small abscesses may be seen.

(2) Parenchymatous myocarditis includes: –

a- Toxic myocarditis:

Causes:

- (i) Severe toxæmia: as in diphtheria, pneumonia, typhoid and severe streptococcal infections. No organism is detected in the heart lesions.
- (ii) Chemical toxins: as carbon monoxide, antimony compounds, arsenic, sulphonamides, phosphorus and chloroform.

Microscopic: There are areas of degeneration e.g. fatty change, in the myocardial fibres, with interstitial oedema and cellular infiltration by lymphocytes, plasma cells, eosinophils, polymorphs and macrophages.

In severe cases, as in diphtheria, there are vacuolations and necrosis of the muscle fibres, especially in the conduction system of the heart.

b- Protozoal myocarditis:

- **Toxoplasma gondii** (household cats are the most common vector) also can cause myocarditis, particularly in immunocompromised persons. About 50% of the fatal cases of congenital toxoplasmosis, show myocarditis.

Microscopic: The myocardium shows diffuse inflammatory infiltration by lymphocytes, eosinophils and histiocytes. The cysts of toxoplasma are usually seen within the muscle fibres.

- **Trichinosis** is the most common helminthic disease with associated cardiac involvement.

(3) Interstitial (viral) myocarditis: – –

It is seen more often nowadays.

Causes:

Viral infections are the most common cause of myocarditis in United States.

- **Coxsackie viruses A and B** and enteroviruses accounting for a majority of the cases.
- **Cytomegalovirus (CMV)**, human immunodeficiency virus (**HIV**) and influenza viruses are less common pathogens.
- In most cases the injury results from an immune response directed against virally infected cells.

Microscopic: There is diffuse interstitial inflammation with infiltration by lymphocytes, plasma cells and macrophages (*Fig. 1.32*). Focal myocardial necrosis is common in severe cases.

Effect: Death occurs in severe cases.

(4) Granulomatous myocarditis:

a- **Rheumatic myocarditis.**

b- **Tuberculous myocarditis:** It is rare and may take the form of:

- Tuberculoma: It appears as one or multiple, rounded, firm yellow caseous nodules and tubercle formation. They are more frequent in the interventricular and interatrial septa.
- Miliary tuberculosis: It is a part of generalized miliary tuberculosis.
- Diffuse tuberculous myocarditis: It is very rare.

c- **Syphilitic myocarditis:** It is very rare and appears as:

- Diffuse interstitial syphilitic myocarditis; in the new born in congenital syphilis.
- Localised gumma: In adults, usually affecting the interventricular septum, resulting in heart block.

d- **Fungal myocarditis:** It is rare especially cryptococcal, aspergillus and monilial myocarditis. They are more commonly seen during therapy of malignant tumours especially lymphomas and leukemias.

e- **Sarcoidosis:** It is also rare and usually affects the conduction system, which shows the typical sarcoid reaction

f- **Idiopathic giant cell myocarditis:**

- It is a rare rapidly fatal disease of sudden onset
- Affects young adults and is of unknown cause.
- In most cases, the heart is only involved especially the ventricular myocardium, which shows large areas of complete necrosis. At the periphery, there is marked mononuclear cellular infiltration with many elongated giant cells (*Fig. 1.33*).
- Some cases are seen with thymomas and Wegener's granulomatosis, chronic rheumatic valve disease and are seen in cases dying during mitral valvotomy.
- It may represent the aggressive end of lymphocytic myocarditis.
- It carries a poor prognosis.

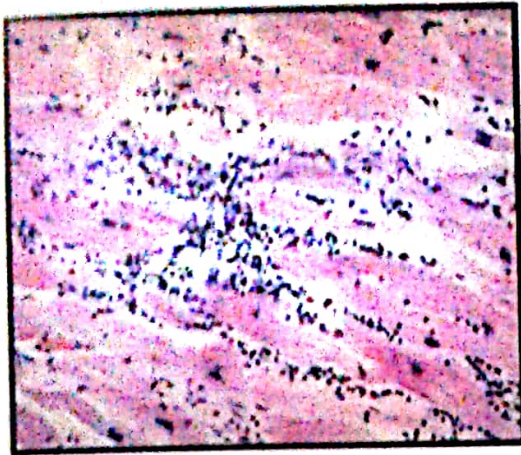


Fig.1.32: Viral myocarditis

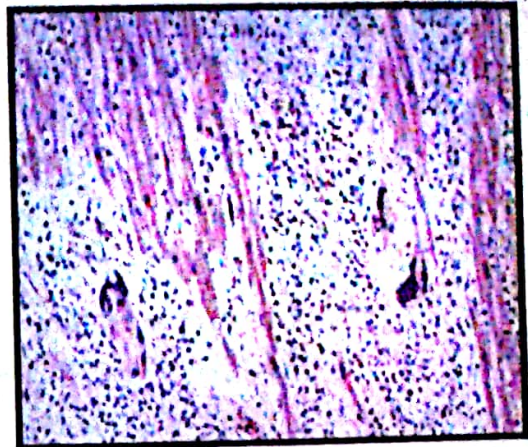


Fig.1.33: Giant cell myocarditis



Fig. 1.34: Acute suppurative pericarditis.



Fig. 1.35: Cardiac myxoma,

Pericarditis

Pericarditis means inflammation of the pericardium.

Types:

A- Acute pericarditis:

1- Serous pericarditis:

Causes:

- Viral (infections (e.g. Cocksackie virus B, Echovirus, mumps and Influenza).
- Non-bacterial (inflammation as; rheumatic fever, SLE and systemic scleroderma.
- Idiopathic.

Fate: It resolves spontaneously in days or weeks.

It usually does not encroach upon the cardiac function.

2. Fibrinous or serofibrinous pericarditis.

It is the commonest form of pericarditis (Fig. 1.21):

- Causes:**
- Rheumatic fever.
 - Myocardial infarction.
 - Uraemia.
 - Trauma.
 - Lung diseases as pneumonia.

Fate:

- Resolution with digestion of the fibrin.
- Organization leads to mild adhesive pericarditis or only plaque like fibrous thickening of serosal membranes.

3. Suppurative or purulent pericarditis (Fig. 1.34):

It is infection of the pericardial space by bacteria or fungi.

Causes:

- a. Direct extension of infection from; pneumonia, empyema, mediastinal infection, osteomyelitis of ribs, subphrenic abscess or myocarditis.
- b. Blood-borne infection as in septicaemia or pyaemia.
- c. Lymphatic: subphrenic or hepatic abscess.
- d. Penetrating chest wound.

Fate: The outcome is organization with marked adhesions resulting in mediastino-pericarditis or constrictive pericarditis.

4. Haemorrhagic pericarditis:

It denotes inflammatory exudates mixed with blood.

Causes:

- T.B.

- Malignant neoplasms
- Pericarditis in patients with underlying blood disease
- Severe bacterial infections.

Fate: The outcome is as suppurative pericarditis.

NB: It must be differentiated from haemopericardium in which the fluid is purely blood of non-inflammatory origin

B. Chronic pericarditis:

1. Tuberculous Pericarditis:

Causes:

- a- Blood borne.

- b- Direct extension or by lymphatic from pulmonary tuberculosis or tuberculous mediastinal lymph nodes.

Microscopic: It appears as fibrinous inflammation with granulation tissue, tubercles and sometimes areas of caseation.

Occasionally the exudate may be haemorrhagic.

Fate: Healing by organization results in constrictive pericarditis or adherent mediastinopericarditis.

C. Healed pericarditis:

- ⊙ Adhesive pericarditis: In which there is delicate adhesions either diffuse or focally obliterating the pericardial sac.

It rarely causes impairment of cardiac function.

- ⊙ Constrictive pericarditis:

It means the formation of dense fibrous or fibrocalcific scar around the heart, causing severe cardiac dysfunction.

It follows suppurative or haemorrhagic pericarditis.

The heart is small and cannot expand adequately during diastole. Constriction of the venae cavae during the fibrotic process may block the venous return leading to congestive heart failure.

Pericardial effusions:

It means accumulation of fluid in the pericardial sac.

A- Hydropericardium (serous):

It is the accumulation of transudate in the pericardial sac.

Causes: It occurs in generalized oedema e.g. cardiac, renal and nutritional.

Fate: Absorption occurs with removal of the causes leaving a normal pericardium.

B- Haemopericardium:

Pure blood or serosanguinous fluid in the pericardial sac.

Causes:

1. Rupture of the heart:

a- Traumatic - e.g. stab wound.

b- Spontaneous - e.g. myocardial infarction. ←

2. Rupture of the intrapericardial portion of the aorta:

a- Aortic dissection. ←

b- Syphilitic aneurysm. ←

c- Traumatic. ←

3. In haemorrhagic diatheses; e.g. purpura, hypo-prothrombinaemia, scurvy and anticoagulant therapy.

Fate: In most cases, death occurs rapidly due to cardiac tamponade, as little as 200 -300 ml commonly being fatal.

C- Chylous effusion: Occurs in case of mediastinal lymphatic obstruction.

Pneumopericardium:

It denotes the presence of air in the pericardial sac.

Causes:

1. Trauma.
2. Perforation of the lung or the oesophagus into the pericardium.
3. Pericarditis due to gas-forming organisms.

Heart Failure:

Heart failure is a state in which the ventricular myocardium fails to maintain a circulation adequate for the needs of the body despite adequate venous filling pressure.

It is generally referred to as *congestive heart failure*.

Most cases of heart failure are due to;

- 1- Systolic dysfunction i.e., inadequate myocardial contractile function, in ischemic heart disease or hypertension.
- 2- Diastolic dysfunction i.e., inability of the heart to adequately relax and fill, as in massive left ventricular hypertrophy, myocardial fibrosis, amyloid deposition, or constrictive pericarditis.
- 3- Valve dysfunction (e.g., due to endocarditis).

- Myocardial hypertrophy and cardiac dilatation may compensate for decreased myocardial contractility.
- When the myocardial fibres are dilated and stretched, the heart contracts with greater force however when the fibres are overstretched the overdilated ventricle responds by decreasing stroke volume and cardiac output.
- The heart fails only when the blood supply is inadequate for the needs of the hypertrophied myocardium and the reserve power of the heart muscle is exhausted due to over stretch of the muscle fibres.

I- Acute heart failure:

Occurs when the causal factor develops suddenly or rapidly. Sudden death due to acute heart failure is due to the following **causes**:

- (1) Massive pulmonary embolism.
- (2) Sudden occlusion of a main coronary artery leading to ventricular fibrillation.
- (3) Acute toxic myocarditis: complicating severe acute infections with marked toxæmia as in diphtheria.
- (4) Haemopericardium with cardiac tamponade.

II- Chronic heart failure:

Occurs when the causal factors develop slowly.

Types:

a. Left sided heart failure (left ventricular failure):

Causes:

- (1) Coronary heart disease.
- (2) Hypertension.
- (3) Mitral incompetence. (MI).
- (4) Aortic valve disease (stenosis or incompetence).
- (5) Coarctation of the aorta.

Effects: They are mostly on the lungs, but the function of the kidneys and brain may be also impaired.

Lungs: Show the picture of chronic venous congestion followed by pulmonary oedema. Sometimes pleural effusion occurs:

- (1) The earliest complaint of the patient is dyspnea on exertion followed by shortness of breath even at rest.
- (2) A characteristic symptom is paroxysmal nocturnal dyspnea i.e. sudden onset of respiratory distress which wakes the patient from sleep. In advanced cases the patient becomes unable to sleep at all in the recumbant position i.e. he becomes orthopneic.

Kidneys: The glomerular filtration rate falls due to decreased blood flow to renal arteries with salt and water retention. Generalized oedema may develop.

Brain: Cerebral hypoxia may give rise to irritability and restlessness.

b. Right-sided heart failure (right ventricular failure):

Causes:

- (1) Mitral stenosis.

(2) Chronic lung diseases as:

a- Emphysema.

b- Ayerza's disease (bilharzial or syphilitic).

c- Pulmonary fibrosis due to tuberculosis, silicosis and bronchiectasis.

(3) Left sided heart failure.

(4) Pulmonary stenosis or incompetence.

(5) Congenital heart diseases as: Fallot's tetralogy and VSDs.

Effects:

(1) Chronic venous congestion all over the body.

(2) Cardiac oedema and ascites.

(3) Brain hypoxia.

NB: Respiratory symptoms in contrast to left-sided failure may be absent or insignificant. [Cyanosis] is much more intense than dyspnea.

c. Congestive (biventricular) heart failure.

It develops usually in cases of left ventricular failure.

Both ventricles may fail simultaneously as a result of:

- Diffuse or extensive myocardial damage e.g. extensive infarction, severe myocarditis and congestive cardiomyopathy.
- Conditions which increase the work load of both ventricles e.g. lesions of mitral and aortic valves.
- Raised cardiac output such as thyrotoxicosis, anaemia and congenital anomalies with left to right shunts.

Cardiac tumours

1- **Primary cardiac tumors are uncommon:**

a- **Benign tumours:** Myxoma (Fig.1.35), mainly in the left atrium, lipoma, fibroma, and rhabdomyomas.

b- **Malignant tumours:** Angiosarcomas constitute the most common primary malignant tumour of the heart.

2- **Secondary neoplasms:**

- Metastases constitute the most common malignancy of the heart.
- In descending order metastasis are lung cancer, lymphoma, breast cancer, leukemia, melanoma, hepatocellular carcinoma, and cancer colon.

SUMMARY

Diseases of the blood vessels:

Atherosclerosis: Definition, pathogenesis, morphology and complications.

Hypertension: Definition, classifications, morphological changes and complications.

Aneurysms: Definition, types and complications.

Dissections: Definition and complications.

Vasculitis: Is inflammation of the vessel wall, causes and types.

Diseases of the heart:

Congenital heart diseases:

Left to right shunts: ASDs, VSDs or a PDA.

Right to left shunts: Fallot's tetralogy or transposition of the great vessels.

Obstructive lesions include coarctation of the aorta.

Ischaemic heart diseases (IHD):

Cardiac ischemia: causes; types of angina.

Myocardial infarction: definition; morphology and complications of MI.

Systemic hypertensive heart disease: produces hypertrophy of the left ventricle, dilataion and CHF occurs.

Pulmonary hypertensive heart disease (Cor Pulmonale)

Rheumatic Fever: definition, pathogenesis, morphology & complications.

Endocarditis: Acute and subacute infective endocarditis, non-bacterial thrombotic endocarditis, atypical verrucous endocarditis; and valvular lesions in carcinoid tumour and syndrome.

Cardiomyopathies: Hypertrophic, dilated and restrictive cardiomyopathies; causes, morphology and complications.

Myocarditis: is myocardial damage secondary to infections or immune reactions; suppurative, toxic, protozoal, viral, TB, and fungal myocarditis.

Pericarditis and Pericardial effusions: definition and types.

Cardiac Tumours: Primary: Benign myxoma and malignant angiosarcomas. Secondaries constitute the most common malignancy of the heart.

Chapter 2

Diseases of Respiratory System

Intended Learning Outcomes (ILOs):

By the end of this unit the students will be able to:

- ☐ Describe the pathologic features of **nasal polyps**.
- ☐ Describe the pathologic features of **tonsillitis** and **diphtheria**, explain pathogenesis, and list complications.
- ☐ Classify **laryngeal tumours**, list the precancerous factors and describe the pathologic features of laryngeal squamous cell carcinoma.
- ☐ Compare between **obstructive and restrictive lung diseases**.
- ☐ Define and classify **emphysema**, explain its pathogenesis, describe its pathologic features and list its complications.
- ☐ Define **chronic bronchitis**, list its types and describe its pathologic features and clinical course. Define Reid Index.
- ☐ Define **bronchial asthma**, explain pathogenesis and describe the pathologic features and compare between intrinsic and extrinsic asthma.
- ☐ Define **bronchiectasis**, list predisposing factors, explain pathogenesis and describe pathologic features and complications.
- ☐ Define **pneumonia**, describe the gross and microscopic picture of the classical pathologic stages of acute lobar pneumonia.
- ☐ Compare between lobar pneumonia, bronchopneumonia.
- ☐ Enumerate **suppurative lung diseases**.
- ☐ Identify types of **pulmonary tuberculosis**.
- ☐ Describe the pathological features of secondary pulmonary TB.
- ☐ Define **lung collapse**, describe its gross and microscopic pictures and explain its different types.
- ☐ Define **pneumoconiosis** and compare the different types.
- ☐ Define **acute respiratory distress syndrome (ARDS)**.
- ☐ Classify **lung tumours**, recognize the predisposing factors and its relation to cigarette smoking.
- ☐ Compare the different types of **bronchogenic carcinoma**.
- ☐ Recognize **lung hamartoma**, **carcinoid tumour** and describe their pathological features.
- ☐ Analyze and diagnose a pathologic condition based on given clinical, radiologic data and / or laboratory findings.
- ☐ List the possible causes of **pleural effusions**.
- ☐ Define **pneumothorax** and describe the different possible types.
- ☐ Describe **malignant mesothelioma** and its pathologic features.

DISEASES OF THE RESPIRATORY SYSTEM

The respiratory system is divided into a conducting portion and a respiratory portion. The conducting portion includes (nasal cavity, larynx, pharynx, trachea, bronchi, bronchioles and terminal bronchioles). The respiratory portion includes respiratory bronchioles, alveolar ducts and alveolar sacs.

The main function of the respiratory system is to exchange carbon dioxide for oxygen.

Diseases of the nose

Rhinitis:

It is inflammation of the mucous membrane of the nose which may be acute or chronic.

I- Acute rhinitis; is a common disease, may be viral as in common cold.

II- Chronic rhinitis; may be specific or non specific.

1- Chronic specific rhinitis (granulomas): Including syphilis, tuberculosis, leprosy and rhinoscleroma.

2- Chronic non specific rhinitis: Appears in one of two forms:

a- Chronic hypertrophic rhinitis:

Repeated attacks of allergic inflammation result in chronic changes in the nasal mucosa i.e. it becomes hypertrophied, thickened, and polypoid.

Nasal Polyp:

Nasal polyps are not true neoplasms, they may develop as a result of chronic inflammation, due to; asthma, recurring infection, allergies, drug sensitivity or certain immune disorders.

Gross: They are soft polypoid masses protruding from the nasal mucosa.

Microscopic: Nasal polyps are formed of:

- Loose mucoid oedematous stroma containing mucus glands and infiltrated with eosinophils, lymphocytes, plasma cells, macrophages, neutrophils and mast cells.
- They are covered by respiratory epithelium showing hyperplasia, ulceration or squamous metaplasia.

- b- *Chronic atrophic rhinitis*: Is a rare disease of unknown cause, more common in females. The nasal mucosa is atrophic, with offensive odour and loss of sensation of smell due to atrophy of the nerve endings.

Tumours of the nose:

- a- *Benign tumours*: are rare as papilloma, adenoma, fibroma, lipoma, haemangioma, chondroma and osteoma.
- b- *Malignant tumours*: are rare and appear as squamous cell carcinoma, fibrosarcoma and chondrosarcoma.

Epistaxis:

It denotes bleeding from the nose.

Causes:

a- *Local causes*: such as

1. All types of rhinitis (acute and chronic, specific and non-specific).
2. All benign and malignant tumours of the nose.
3. Trauma, especially when there is congenital telangiectasia.

b- *General causes*:

1. Hypertension.
2. Infectious fevers as typhoid and measles.
3. Scurvy (Vitamin C deficiency)
4. Vitamin K deficiency.
5. Blood diseases as haemophilia, purpura and leukaemia.

Diseases of the tonsils

Tonsillitis:

It means inflammation of the tonsils; it may be acute or chronic.

Acute tonsillitis:

- The commonest organism is the haemolytic streptococcus.
- The infection is accompanied by fever, tachycardia, leucocytosis, and enlargement of the cervical lymph nodes.

Acute tonsillitis may be:

- 1- *Acute follicular tonsillitis*: Suppurative inflammation confined to the lymphoid follicles. Pus accumulates in the crypts and appears on the surface as yellowish dots (Fig.2.1).
- 2- *Acute parenchymatous tonsillitis*: Suppurative inflammation is diffuse in the tonsils and surrounding tissues.

Chapter 2: Diseases of the respiratory system

3. Peritonsillar abscess (Quincy): Is a rare condition in which an abscess forms in the tonsil and peritonsillar tissue. It is usually unilateral.

Complications of acute tonsillitis:

1. Spread of infection to the surrounding tissues, as the ear.
2. Chronic tonsillitis; due to repeated infections.
3. Rheumatic fever or diffuse glomerulonephritis may follow after two weeks.

Chronic tonsillitis: may be

1. Chronic non specific tonsillitis: is a common condition, due to repeated attacks of acute suppurative tonsillitis.
2. Tuberculosis of the tonsils: occurs rarely as a primary condition.

Diphtheria:

It is an infectious local membranous inflammation in the upper respiratory tract (rarely in the upper gastrointestinal tract) with systemic dissemination of toxin that evokes lesions in different organs.

- Affects mainly children.
- Caused by the strongly exotoxic corynebacterium diphtheriae.
- The usual portal of entry is the oral cavity.
- The incubation period varies from one day to seven days.
- Diphtheria is controlled by mass immunization.

Pathological features:

1. Oedema and hyperaemia of the affected epithelial surface appears first.
2. Necrosis of the epithelium accompanied by outpouring of large amount of fibrino-suppurative exudate occurs in the next few days due to elaboration of toxins.
3. The exudate admixed with the necrotic mucosa creates a tough, dirty, grey superficial pseudomembrane.

Complications:

1. Laryngeal obstruction due to oedema of the larynx and peripheral neuritis.
2. Suffocation which may be fatal unless tracheostomy is done. It is due to separation of a part of the pseudo-membrane obstructing the air passages.
3. Toxaemia and its manifestations (See general pathology).

Diseases of the larynx

Laryngitis:

Laryngitis is a non-inflammatory reaction to injury due to smoking or abuse of voice. It presents by hoarseness of voice.

A. Acute laryngitis: May be bacterial as in diphtheria, or viral as in common cold, or due to irritation by fumes, or abuse of voice.

B. Chronic laryngitis: may be

- Specific: as in T.B., Syphilis, laryngoscleroma.
- Non specific: due to smoking, or on top of acute inflammation, or abuse of voice (singer's nodule).

Laryngeal Polyp (Nodule):

It is a non-inflammatory reaction to injury due to smoking or abuse of voice. It presents by hoarseness of voice.

Gross: It appears as hemispherical protrusion or elevation about 0.5cm in diameter, presents on the vocal cords. It may be bilateral.

Microscopic:

- Early stage: Polypoid tissue showing oedematous stroma and proliferated fibroblasts.
- Late stage: The stroma becomes hyalinized with the presence of dilated blood vessels.

Oedema of the larynx:

It is a serious condition which may be a fatal due to suffocation. It is caused by angioneurotic oedema, allergy and inhalation of irritant gases.

Tumours of the larynx:

I. Benign tumours:

a- Squamous cell papilloma:

- It is a small tumour liable to ulceration, haemorrhage or malignant changes which arises from the vocal cords as one or multiple sessile or pedunculated papillomata.
- In children: usually multiple, of viral origin, and recurs after removal.
- In adults: usually single.

b- Fibroma, haemangioma and chondroma.

II. Malignant tumours:

Carcinoma of the larynx: (Primary malignant tumour)

- Represents 2 % of all cancers and 95% of laryngeal malignant tumours.
- Commonly occurs in males above the age of 50 years.

Precancerous lesions:

- Excessive smoking, alcohol and asbestos exposure.
- Human papilloma virus has been detected in 15% of tumours.

Types of laryngeal carcinoma according to anatomical sites: (Fig. 2.2)

Glottic (Intrinsic) (60 - 75%)

- Arises directly from true vocal cords. It is slowly growing and sends late metastasis.
- Usually well to moderately differentiated with sparse lymphatics.
- The prognosis is rather good.
- Interferes with vocal cord mobility (symptomizes early).

Supraglottic (Extrinsic) (30%-35%).

- Arises above the true vocal cords from the epiglottis and epiglottic folds.
- It is usually poorly differentiated.
- Rich in lymphatics. Nearly 1/3 of these tumours metastasize early to cervical lymph nodes.

Subglottic (5%):

- It arises below the vocal cords.
- Tends to remain clinically quiescent until it presents as advanced disease

Gross: It begins as a small nodule, and then it enlarges as a fungating or ulcerating mass.

Microscopic: Squamous cell carcinoma of various grades of differentiation.

Complications of cancer larynx:

1. Haemorrhage, ulceration, infection and obstruction.
2. Lung abscess and bronchopneumonia due to aspiration of septic material from the infected necrotic tumour tissue.
3. Effects of metastases:
4. Cancer cachexia (weakness, anaemia and wasting).

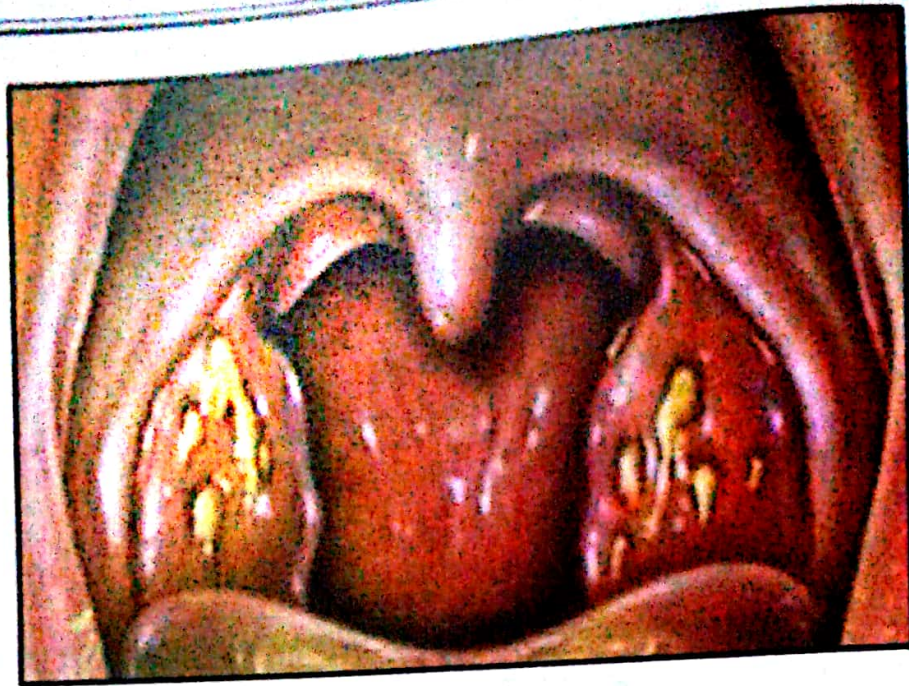


Fig. 2.1: Acute follicular (suppurative) tonsillitis.

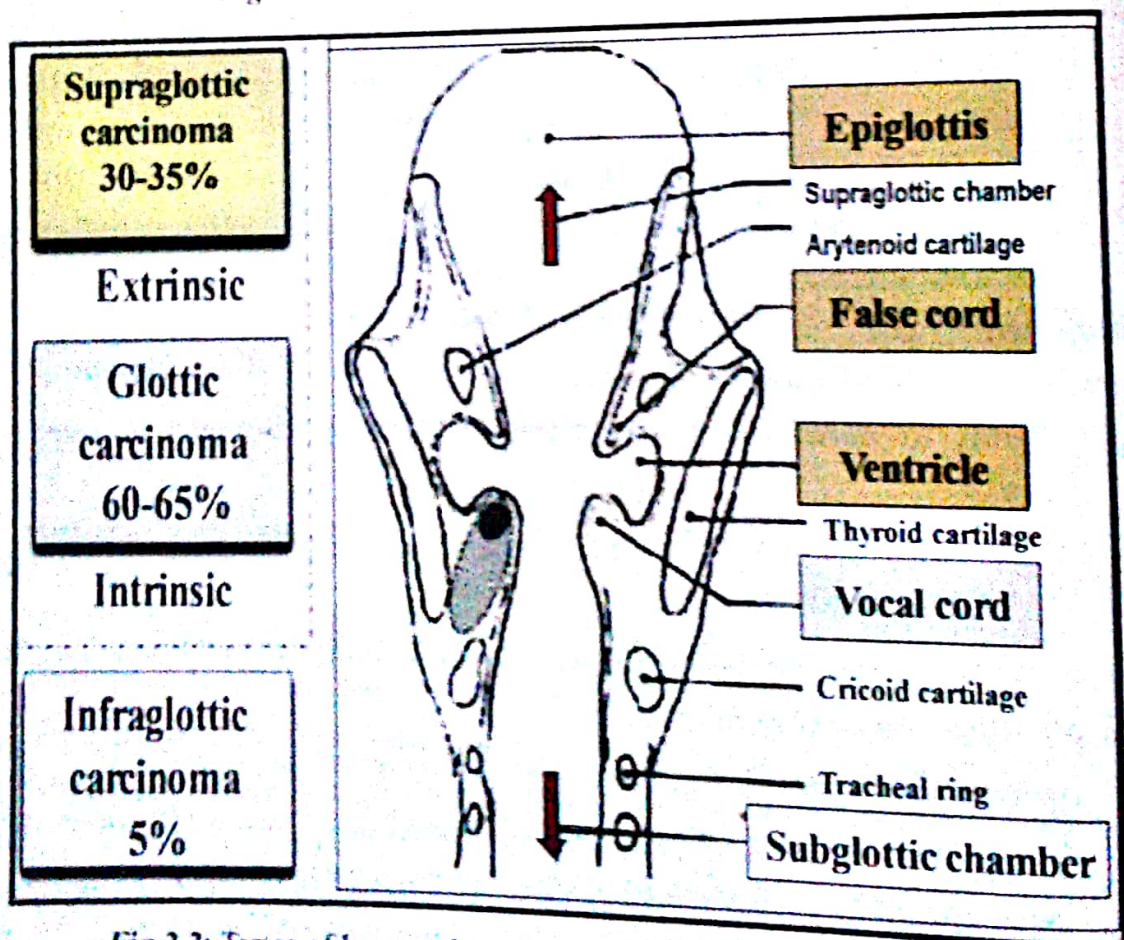


Fig. 2.2: Types of laryngeal carcinoma according to anatomical sites.

Diseases of the lungs

Diffuse pulmonary diseases can be classified into 2 categories:

Obstructive Disease	Restrictive Disease
It is characterized by <i>increased resistance to airflow</i> due to partial or complete obstruction at any level.	It is characterized by <i>reduced expansion of lung parenchyma</i> with decreased total lung capacity.
1. Emphysema (loss of elastic recoil) 2. Chronic bronchitis (both 1 & 2 are called COPD) 3. Bronchial asthma (airway narrowing) 4. Bronchiectasis 5. Cystic fibrosis	1- Acute and chronic interstitial lung diseases e.g acute respiratory distress syndrome and chronic diseases as pneumoconiosis, sarcoidosis & idiopathic pulmonary fibrosis. 2 -Extra pulmonary disorders e.g. obesity, poliomyelitis & kyphoscoliosis

1- Obstructive Lung diseases:

Chronic obstructive pulmonary diseases (COPD):

- Affect about 10% of population.
- They are the 4th leading cause of death.
- Include; emphysema and chronic bronchitis.

Microanatomy of the terminal air passages:

1. The large bronchi divide into smaller bronchi which branch and give rise to bronchioles.
2. The terminal bronchiole is the 1st small bronchiole not to bear alveoli, it branches into respiratory bronchioles with alveoli arising from their walls. The respiratory bronchioles may branch 3 - 5 times.
3. Eventually the respiratory bronchioles form alveolar ducts whose walls are lined entirely by alveoli.
 - The respiratory acinus; is the fundamental unit of the lung. It is the portion of lung tissue formed by the branching of a single terminal bronchiole as just described (*Fig.2.3*).
 - The lung lobule is a hexagonal area of the lung and it is supplied by 3 - 5 terminal bronchioles which radiate from the center.

Pulmonary emphysema:

It is abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls without significant fibrosis.

- Emphysema is one of the main diffuse obstructive airway diseases characterized by limitation of maximal airflow rates during forced expiration due to loss of elastic recoil.
- Expiratory airflow obstruction may result from airway narrowing as in asthma or from loss of elastic recoil which characteristically occurs in emphysema.

Incidence of emphysema:

- It is a common disease. 80% of adult's autopsy specimens show emphysema and were asymptomatic.
- Centrilobular emphysema is most common (more than 95% of cases) and related to heavy smoking.
- The centrilobular and panlobular types cause clinically significant obstruction.

Types of emphysema (Fig. 2.4):

1- Centrilobular emphysema:

- Common in male smokers.
- The lesions are more common and more severe in the upper lobes.
- The central or proximal part of the acini formed by the respiratory bronchioles are affected while the distal alveoli are spared.
- Patients tend to have chronic hypoxia and a raised partial pressure of CO_2 ($PACO_2$) and this leads to pulmonary hypertension and right ventricular failure.

2- Panacinar (Pan-lobular) emphysema:

- The acini are uniformly affected from the level of the respiratory bronchioles to terminal blind alveoli; i.e. involves the entire acinus.
- Common in lower lung zones.
- Occurs in patients with alpha 1-anti-trypsin deficiency.
- The lungs are voluminous.

3- Distal acinar (Para-septal) emphysema:

- Distal part of acinus is involved while the proximal part is normal.
- It is strikingly adjacent to the pleura and at the margins of lobules.
- More severe in upper half of the lung.
- Enlarged airspaces reach 0.5 to 2 cm or may form cyst-like structures (Bullae).

4- Irregular emphysema:

- The acinus is irregularly involved.
- It is the most common form of emphysema, since it is almost associated with scarring. In most cases, it is asymptomatic.

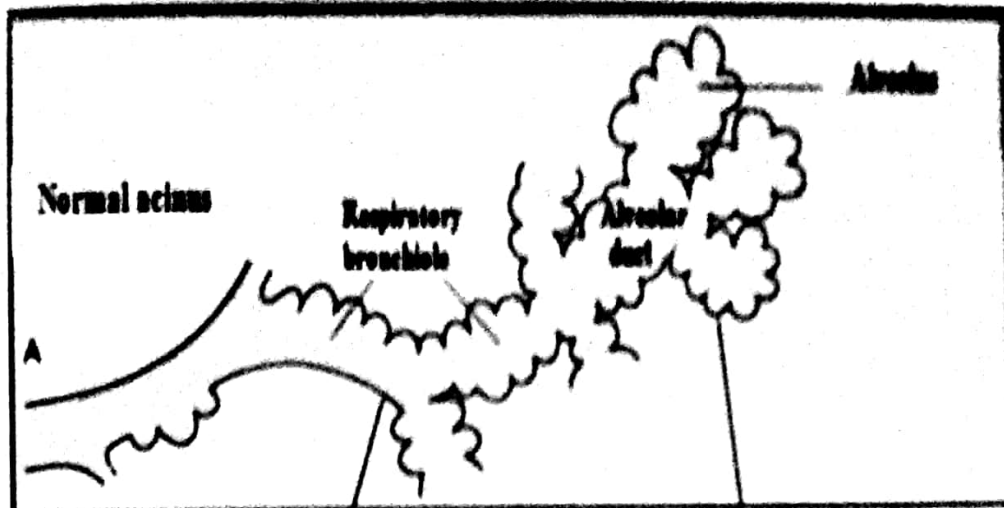


Fig.2.3: Diagram of normal lung acinus

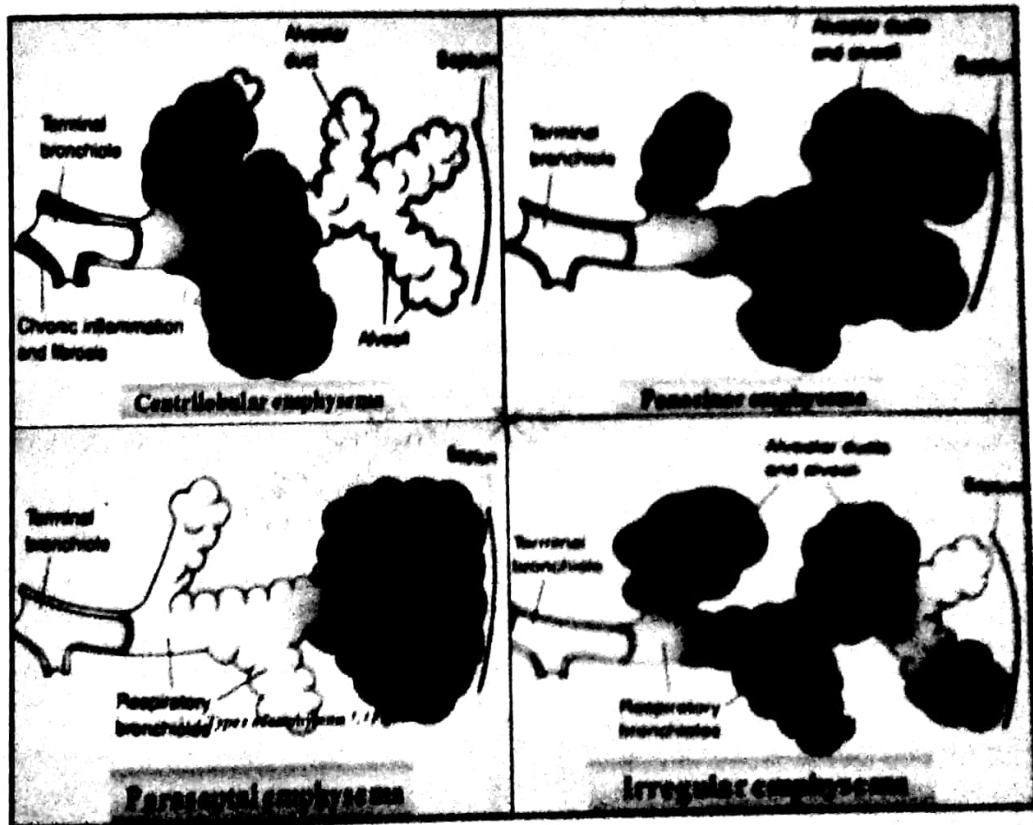


Fig.2.4: Types of emphysema

Pathogenesis of emphysema (Fig.2.5):

- Exposure to toxic substances such as tobacco smoke and inhaled pollutants induces ongoing inflammation with accumulation of macrophages and lymphocytes in the lung.
- Elastases, cytokines (including IL-8) and oxidants are released causing epithelial injury and proteolysis of the extracellular matrix (ECM).
- Elastin degradation products further increase the inflammation.

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- Unless checked by antielastases (e.g., α_1 -antitrypsin) and antioxidants, the cycle of inflammation and ECM proteolysis continues.
- Multiple genetic factors control the response to injury after smoking as **TGF- β gene polymorphisms** lead to inadequate repair of elastin injury caused by inhaled toxins.
- Thus emphysema can be thought of as resulting from insufficient wound repair.

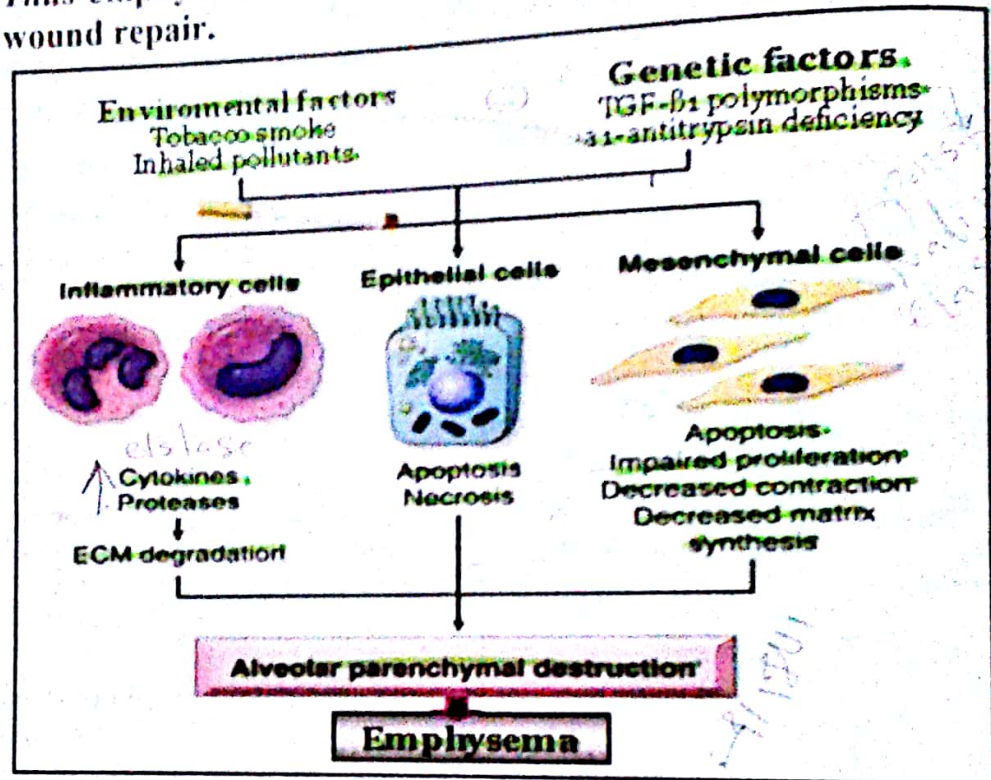


Fig.2.5: Pathogenesis of emphysema

Gross: Lungs are voluminous (more in panacinar). The upper parts are more affected in the centrilobular type. Bullae are characteristic of distal acinar type (Fig.2.6).

Microscopic: Destruction of alveolar walls without fibrosis leading to large airspaces.



Fig.2.6: Emphysema with large apical & subpleural bullae

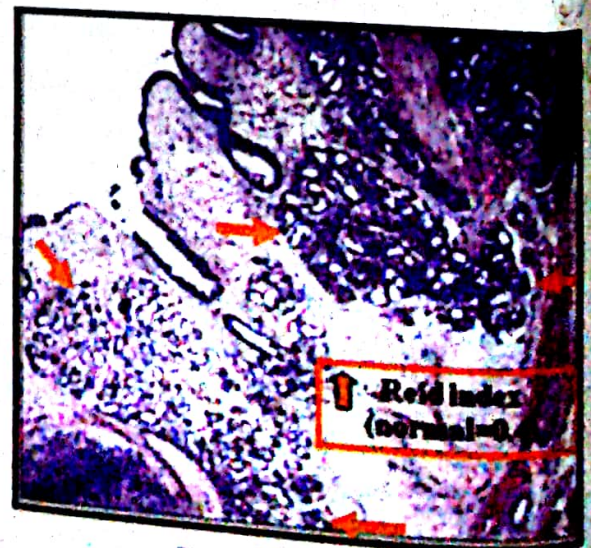


Fig.2.6: Emphysema with

Effects and complications:

1. Dyspnea (progressive), cough and wheezing.
2. Barrel-shaped chest.
3. Cyanosis.
4. Pulmonary hypertension and right side heart failure.
5. Polycythemia.
6. Interstitial emphysema.
7. Pneumothorax due to rupture of emphysematous bullae.

Causes of death in emphysema:

- Right sided heart failure.
- Massive lung collapse due to spontaneous pneumothorax as a result of ruptured emphysematous bullae.
- Respiratory acidosis and coma.

Conditions related to emphysema:

1. Compensatory emphysema:

- It refers to compensatory dilatation of alveoli in response to loss of lung substance e.g. following surgical removal of diseased lung or lobe, near-by area of pneumonia, fibrosis or collapse.

2. Interstitial emphysema:

- It is likely to occur in patients on respirators (ventilators) who have partial bronchiolar obstruction.
- In patients with perforating lung injuries (e.g., a fractured rib).
- Overdistension of alveolar spaces with rupture of their walls, due to combined effect of cough and bronchiolar obstruction which leads to sharply increased pressure within the alveolar spaces as in whooping cough or bronchiolitis.
- As a result of rupture of alveolar wall, blebs of air extend along the fibrous septa of the lung to reach the mediastinum and may extend to the tissues at the root of the neck giving rise to subcutaneous crepitations.

Chronic Bronchitis:-

Clinical definition: It is inflammation of the bronchi with increased mucus production and sputum production for at least 3 months in two consecutive years.

It occurs in several forms:

- Simple chronic bronchitis: Productive cough but no obstruction.
- Chronic asthmatic bronchitis: Chronic bronchitis associated with bronchial asthma.

- Chronic obstructive bronchitis: Chronic bronchitis with outflow obstruction.

Pathogenesis of chronic bronchitis (Fig.2.8)

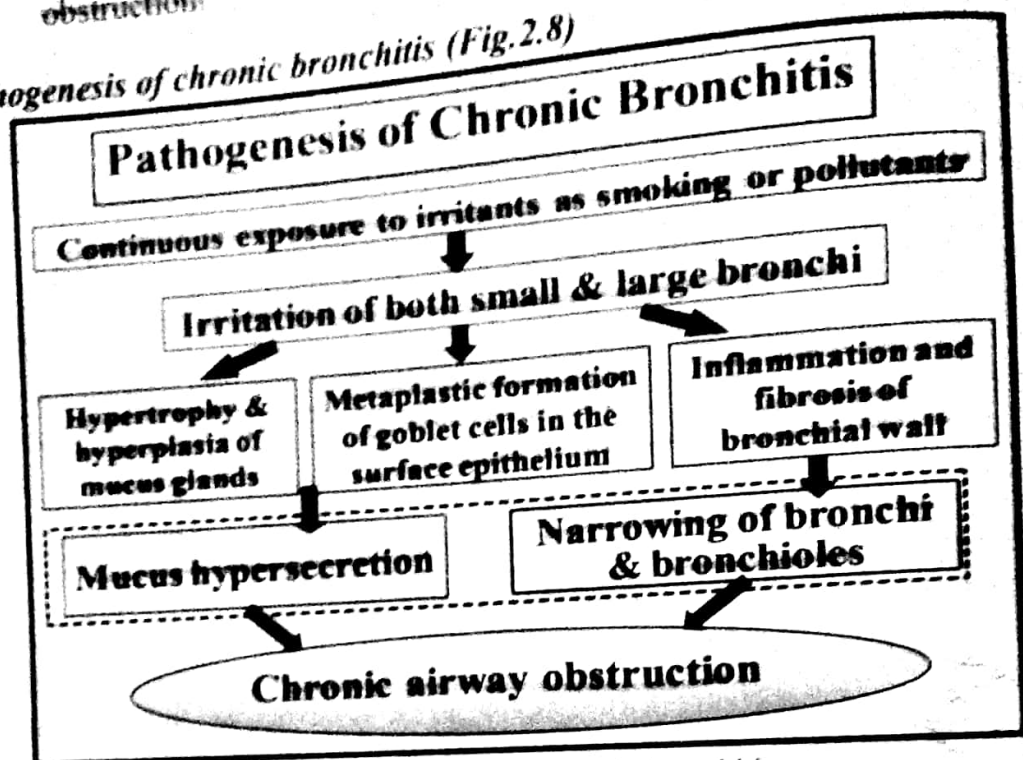


Fig.2.8: Pathogenesis of chronic bronchitis

Gross:

- Hyperaemia and oedema of mucous membranes of the bronchi.
- Excess mucinous secretions or casts filling the airways.

Microscopic (Fig.2.7):

- Epithelial changes as hyperplasia, goblet cell metaplasia and squamous cell metaplasia are common.
- Infiltration of bronchial and bronchiolar walls with chronic non-specific inflammatory cells.
- Enlargement of mucous glands layer with increase in **Reid index** (it is the ratio of thickness of the mucus gland layer to that of the bronchial wall "The Reid index normally 0.4").

Bronchial Asthma:

A chronic inflammatory disorder of the airways characterized by intermittent and reversible airflow obstruction, chronic bronchial inflammation and bronchial hyper-responsiveness.

It is characterized by attacks of expiratory dyspnea, wheezes and cough (due to increased irritability of the tracheobronchial tree to various stimuli).

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resulting in paroxysmal contraction of bronchial airways, which may reverse spontaneously or as a result of treatment.

Types: According to the presence or absence of immune disorder bronchial asthma may be classified into extrinsic and intrinsic types.

<u>Extrinsic asthma:</u>	<u>Intrinsic Asthma:</u>
1. Typically initiated by type IIgE mediated hypersensitivity reaction on exposure to an extrinsic antigen.	1. It is a non-immune mediated disease triggered by a number of stimuli in a susceptible person e.g. respiratory tract infection, chemical irritant or drugs.
2. Starts in the first 2 decades of life.	2. Usually in adult life.
3. Family history.	3. Usually no family history.
4. ↑ Serum levels of IgE & eosinophils.	4. Normal serum levels of IgE.

NB: A person who has extrinsic asthma is also susceptible to develop asthmatic attack when exposed to factors implicated in intrinsic asthma.

Pathogenesis: As a result of antigen antibody reaction, histamine and chemical factors are released resulting in bronchospasm, oedema, mucous secretion and leukocytic infiltration (Fig.2.9 & 2.10).

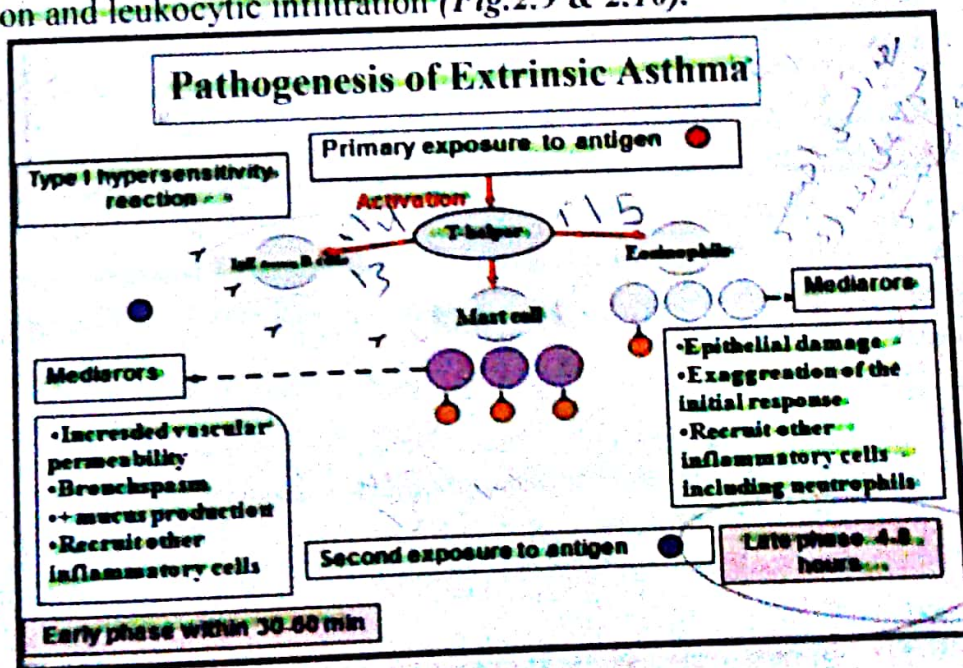


Fig.2.9: Pathogenesis extrinsic asthma

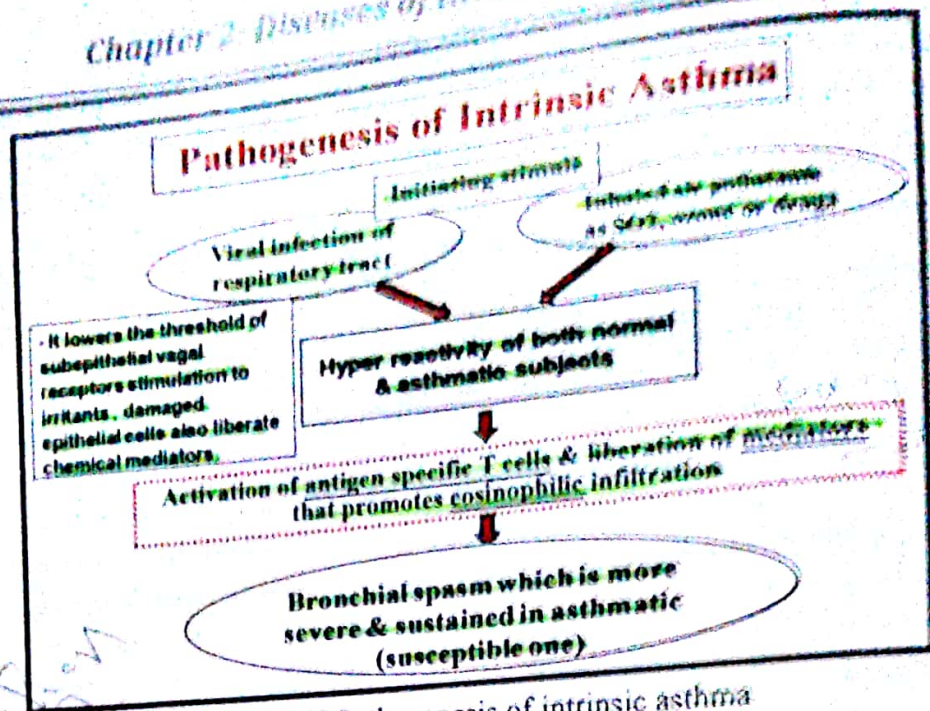


Fig.2.10: Pathogenesis of intrinsic asthma

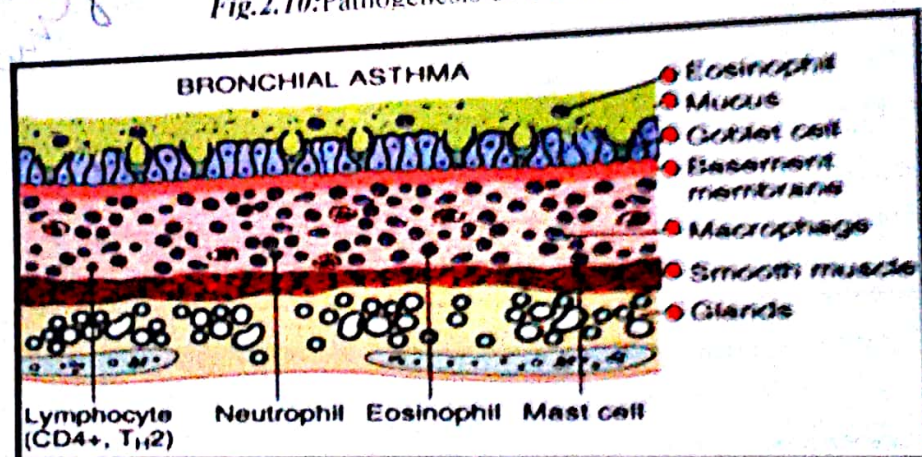


Fig.2.11: Microscopic changes in bronchial asthma

Gross: During attacks the lung becomes over distended with air and shows patchy areas of atelectasis with occlusion of airways by thick tenacious mucous plugs.

Microscopic (Fig.2.11):

- The mucus plugs contain
 - Whorls of shed epithelium (Curschmann spirals)
 - Numerous eosinophils.
 - Charcot-Leyden crystals (crystalloids made of eosinophilic proteins).
- Goblet cell metaplasia in bronchial epithelium.
- Thickening of the basement membrane of the bronchial epithelium.
- Increased submucosal glands with increased vascularity.
- Edema and infiltration of the bronchial wall with inflammatory infiltrate rich in eosinophils.
- Hypertrophy of bronchial smooth muscle.

Bronchiectasis:

It is a permanent dilatation of bronchi and bronchioles caused by destruction of the muscle and the supporting elastic tissue resulting from or associated with chronic necrotizing infections

Predisposing factors:

- 1- Bronchial obstruction by tumors, foreign body or mucus impaction.
Under these conditions bronchiectasis is localized to the obstructed lung segment. Bronchiectasis may also complicate bronchial asthma and chronic bronchitis
- 2- Necrotizing or suppurative pneumonia with virulent organisms. TB is also an important cause of bronchiectasis
- 3- Congenital or hereditary conditions:
 - Cystic fibrosis; the abnormal viscid mucus causes obstruction and infection resulting in widespread severe bronchiectasis.
 - Kartagener syndrome; an autosomal recessive disorder with structural abnormalities of cilia impairing the clearance of mucus leading to recurrent infection. It is characterized by congenital bronchiectasis, frontal sinusitis and dextro-cardia.

Pathogenesis (Fig. 2.12):

- Infection and complete obstruction are the two factors responsible for the production of bronchiectasis.
- Infection results in chronic bronchial wall inflammation ending in fibrosis and weakening of the wall of bronchi.
- If complete obstruction of the lumen of the bronchi occurs due to any cause it results in collapse of alveoli dragging with it the wall of the fibrosed bronchioles leading to their dilatation which is permanent even if complete obstruction is removed.
- Dilated bronchi help accumulation of secretions which adds more to infection and more to fibrosis of the wall adding more to the pathogenesis of bronchiectasis.

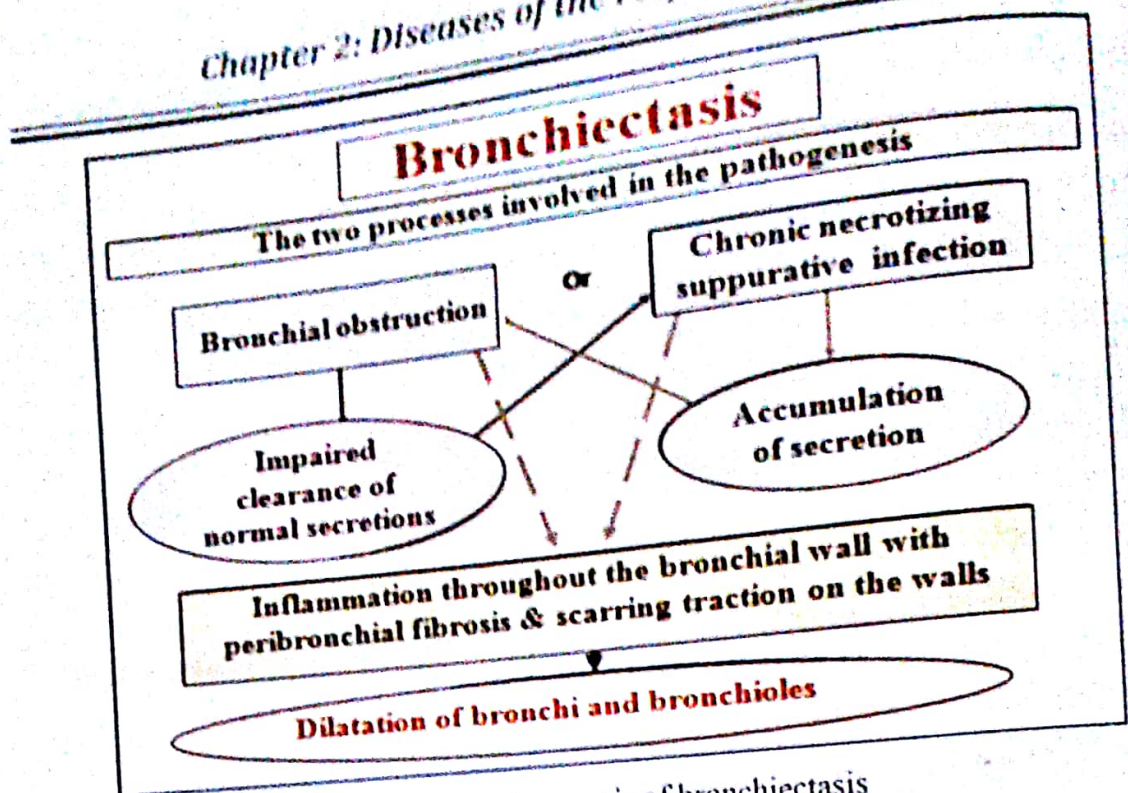


Fig.2.12: Pathogenesis of bronchiectasis

Gross:

- Occurs more commonly in the lower lobes of the lung.
- The bronchi are dilated either diffusely i.e. cylindrical type (more common), or localised i.e. saccular type (less common). The bronchi are usually filled with pus.
- The intervening lung tissue is destroyed and replaced by dense fibrous tissue. The covering pleura may show pleurisy.

Microscopic:

Active phase:

- Bronchi and bronchioles are dilated and filled with acute inflammatory exudate (neutrophils and pus cells).
- Bronchial epithelium may be destroyed resulting in necrotizing ulceration. It may show squamous metaplasia or hyperplasia.
- There is an intense acute and chronic inflammatory exudation within the walls of bronchi.

Chronic phase:

- Fibrosis of bronchial and bronchiolar walls.
- The intervening lung tissue is replaced by fibrous tissue and is infiltrated by chronic inflammatory cells.

Clinical features: Include cough, fever and abundant purulent sputum.

Complications:

1. Cor pulmonale due to excessive fibrosis of the lung.
2. Haemoptysis.
3. Pleural complications: asempyema, pneumothorax, pyopneumothorax and bronchopleural fistula.
4. Lung abscess and gangrene of the lung.
5. Embolic brain abscess.
6. Direct spread of infection leading to mediastinitis and suppurative pericarditis.
7. Malignant transformation into bronchogenic carcinoma on top of squamous metaplasia.
8. Toxaemia, septicaemia and systemic pyaemia.
9. Amyloidosis.

Pneumonia:

It is consolidation of lung tissue due to the presence of an intra-alveolar inflammatory exudate of infective origin.

Classification:

1. Anatomic: lobar pneumonia, bronchopneumonia.
2. Clinical: community-acquired pneumonia, hospital-acquired pneumonia, necrotizing pneumonia, aspiration pneumonia and pneumonia in immuno-compromised host.
3. Aetiologic: bacterial, viral, fungal, rickettsial, chlamydial and protozoal.

I- Bacterial pneumonia:

Depending on bacterial virulence and host resistance, the same organisms may cause bronchopneumonia or lobar pneumonia.

A- Bronchopneumonia:

It is patchy consolidation of the lung, with suppurative inflammation affecting bronchi and surrounding alveoli.

- It is a common disease that tends to occur in extremes of age:
 - In children it usually complicates measles, whooping cough.
 - In old age it complicates diabetes mellitus, malignancies.
- The commonest causative organisms are staphylococci, streptococci, pneumococci and H. influenza.

Gross: (Fig. 2.13).

- The lungs are heavy, dark red, with multiple patches of consolidation of variable size up to 3 to 4 cm in diameter scattered all over the lung.
- The consolidation is often multilobar, frequently bilateral and basal.

Microscopic:

- Suppurative exudate fills the bronchi, bronchioles, and adjacent alveolar spaces.
- The lining epithelium is destroyed and the bronchial walls are infiltrated with polymorphs.
- There is vascular congestion with interstitial haemorrhage.

B- Lobar Pneumonia:

It is acute diffuse fibrinopurulent inflammation affecting a large portion or an entire lobe of lung.

Causative organisms: Most cases are caused by pneumococci, occasionally caused by staphylococci, streptococci and H. influenza.

Predisposing factors:

- It is a disease of young adults and more common in males.
- It usually follows lowering of the resistance as by exposure to cold, fatigue and chronic debilitating diseases.
- Decreased or absent splenic function (e.g., sickle cell disease or after splenectomy); as the spleen contains the largest collection of phagocytes, so it is the major organ for removing pneumococci from the blood. The spleen also produces antibodies against polysaccharides, so help to destroy pneumococci.

Pathologic features (Fig. 2.14, 15):

The following sequence of stages is classic but infrequently seen because of antibiotic therapy.

- Congestion: predominates in the first 24 hours.
- Red hepatization (consolidation): in which the alveoli are filled with fibrinous exudate containing neutrophils and red blood cells giving a red, firm, liver-like gross appearance. The alveolar capillaries are congested and the alveolar walls are thickened.
- Grey hepatization, the red blood cells disintegrate and the remaining fibrinous exudate persists inside the alveoli, giving a greyish brown gross appearance. The alveolar capillaries are congested and the alveolar walls are thickened. The pleura shows fibrinous pleurisy.

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- Resolution is the favourable final stage in which the consolidated exudate is gradually liquified by the proteolytic enzymes of the dead polymorphs and is mainly absorbed by the lymphatics to the bronchial and hilar lymph nodes.

Clinical picture:

- Sudden onset of fever, dyspnea, chest pain and severe cough with small amount of thick rusty sputum.
- If recovery occurs it is suddenly i.e. by crises, after 7 - 8 days.

Complications of bacterial pneumonia (broncho and lobar pneumonia):

1. Abscess formation.
2. Spread of infection to the pleural cavity (empyema).
3. Spread of infection to the pericardium (pericarditis).
4. Destructive lesions of the bronchi producing bronchiectasis.
5. Organization of exudate into fibrotic scar tissue.
6. Bacteraemia with spread of infection leading to meningitis, arthritis, infective endocarditis.

II- Primary Atypical Pneumonia:

Acute febrile respiratory disease characterized by patchy inflammation in the lungs confined to the alveolar septa and pulmonary interstitium.

The designation atypical denotes the moderate amount of sputum, absence of physical findings of consolidation, moderate elevation of white blood cell count.

Aetiology: Causative organisms:

- Mycoplasma pneumonia which is common among children and adults.
- Viruses, including influenza types A and B, respiratory syncytial virus, adenovirus, cytomegalovirus (in immunocompromised patients only) and Chlamydia pneumoniae.

Gross:

- Patchy or it may involve whole lobes bilateral or unilateral with congestion of the trachea and bronchi.
- The affected lobes are red-blue congested and subcrepitant.

Microscopic:

- The inflammatory reaction is confined to the walls of the alveoli. The septa are widened and edematous, infiltrated with mononuclear inflammatory infiltrate of lymphocytes, histiocytes, and occasional plasma cells (Fig.2.16).
- In some cases viral inclusion bodies are seen intranuclearly or intracytoplasmic.
- Alveolar spaces are remarkably free of cellular exudate.
- In severe cases the lung shows interstitial congestion and oedema with diffuse alveolar damage.

Lung abscess:

It is a localized area of suppurative necrosis of lung tissue with cavity formation.

Causative organisms; commonly caused by staphylococci, streptococci, gram-negative organism, and mixed infections.

Abscesses vary in size and number (single or multiple).

Types of lung abscesses:

1. **Aspiration or inhalation abscess:** It is due to aspiration of infected material, as in oropharyngeal surgical procedures, dental sepsis, or aspiration secondary to diminished consciousness from coma, drugs, and anaesthesia. Aspiration of gastric contents is serious because the gastric acidity adds to the irritant role of the food particles.

Gross:

- It is common in the right lung, reflecting the more vertical right bronchus, and is more often single.
 - Acute abscess is rounded, lined by irregular necrotic lung tissue. They contain variable mixtures of pus and air.
 - Chronic abscess is lined by a thick and smooth fibrous wall.
 - The covering pleura shows fibrinous pleurisy or empyema.
2. **Postpneumonic abscess:** Follows broncho or lobar pneumonia (usually multiple and basal).
 3. **Pyæmic abscesses:** As complication of septic emboli from infected thrombi or cardiac valve vegetations (usually small and multiple).

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4. Miscellaneous:

- Direct traumatic penetration of the lung.
- Spread of infection from adjacent organs.
- Pulmonary actinomyces and infected hydatid cyst.
- Neoplasia; secondary infection is common in bronchial obstruction by primary or secondary malignancy.

Complications of lung abscess:

- Pleural complications: Empyema, pneumothorax and pyopneumothorax.
- Haemoptysis.
- Bronchopleural fistula: with serious effects.
- Direct spread of infection leading to mediastinitis and suppurative pericarditis.
- Embolitic brain abscess along the vertebral system of veins.
- Gangrene of the lung.
- Chronicity producing chronic lung abscess.
- Amyloidosis due to chronic toxemia.
- Pyemia.

Gangrene of the lung:

- It is of the moist type.
- The disease is very rare and is usually predisposed to by severe infection of the lung as lung abscess, bronchiectasis and pneumonia, with marked lowering of the resistance as in diabetes, senility and chronic nephritis.
- Superimposed saprophytic infections flourish within the necrotic debris of the abscess cavity.

NB: Suppurative lung diseases include:

- Bacterial pneumonia (mainly bronchopneumonia).
- Lung abscess.
- Empyema and gangrene.
- Bronchiectasis



Fig.2.13: Bronchopneumonia



Fig.2.14: Lobar pneumonia

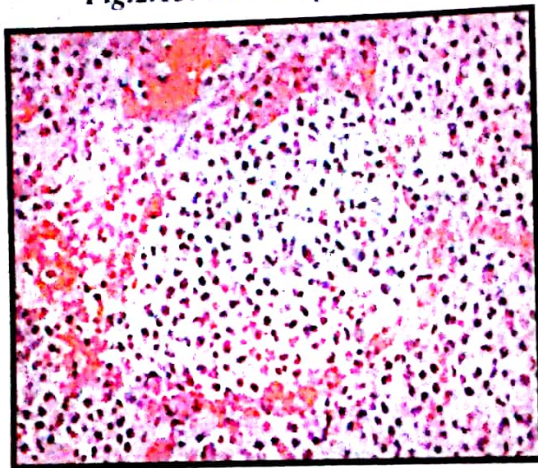


Fig.2.15: Lobar pneumonia

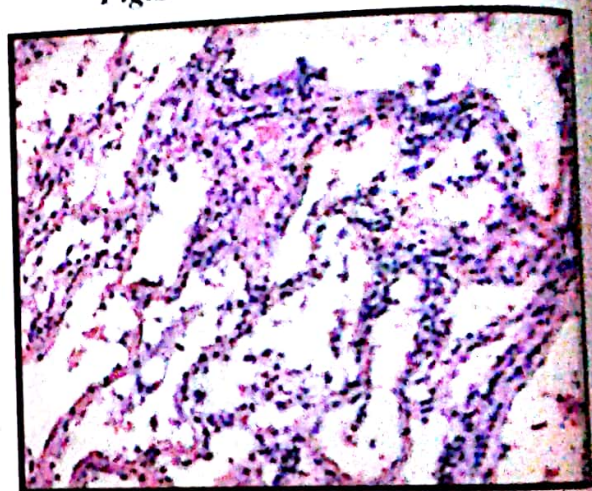


Fig.2.16: Atypical pneumonia



Fig.2.17: Primary pulmonary TB

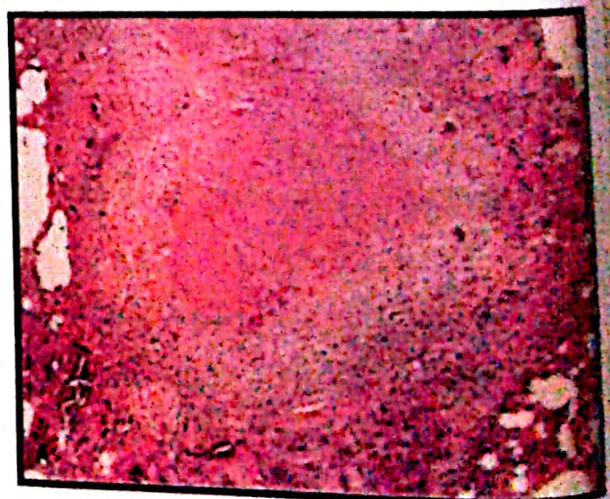


Fig.2.18: Fibrocaceous pulmonary TB

Pulmonary Tuberculosis:

- **Primary tuberculosis** develops in a **previously unexposed** and **unsensitized person** through **exogenous infection**.
- About 5% of those newly infected develop significant disease

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Gross:

- Inhaled bacilli implant in the alveoli in the lower part of the upper lobe or the upper part of lower lobe, usually close to the pleura.

Ghon's focus:

- An area of gray-white inflammatory consolidation (1- 1.5 cm) develops (Fig. 2.17).
- In most cases the center undergoes caseous necrosis and tubercle bacilli drain into the regional nodes, which often caseate.
- This combination of parenchymal lesion and nodal involvement is referred to as **Ghon's complex**.
- In approximately 95% of cases, development of cell-mediated immunity controls the infection. Ghon's complex undergoes progressive fibrosis, followed by radiologically detectable calcification.
- Individual tubercles are microscopic; when multiple tubercles coalesce that they become macroscopically visible.

Microscopic:

- Characteristic granulomatous inflammatory reaction in the form of both caseating and noncaseating tubercles.
- The granulomas are formed of epithelioid cells and multinucleated giant cells enclosed within an outer mantle of lymphocytes and fibroblasts.
- The characteristic central caseation is seen in individuals who have developed cell-mediated immunity to the organism.

The Major Consequences of Primary Tuberculosis are:-

- 1- Induction of hypersensitivity and increased resistance.
 - 2- Foci of scarring harboring viable bacilli for years, and remain as a nidus for reactivation at a later time when host defenses are compromised.
 - 3- The disease may develop progressive primary tuberculosis in individuals who are immunocompromised (as in AIDS or in malnourished children or in elderly).
- ✓ Progressive primary tuberculosis resembles an acute bacterial pneumonia, with lower and middle lobe consolidation, hilar lymphadenopathy and pleural effusion. Cavitation is rare.

- dissemination is a dreaded complication and may result in the development of tuberculous meningitis and miliary tuberculosis.

Secondary tuberculosis (Reactivation TB):

- Secondary tuberculosis is the pattern of disease that arises in previously sensitized host. It may result from:
 - Primary tuberculosis.
 - Reactivation of dormant primary lesions.
 - Exogenous reinfection.
- Reactivation of endogenous tuberculosis occurs when host resistance weakened. It is more common in low-prevalence areas, where reinfection plays an important role in regions of high contagion.
- Less than 5% with primary disease subsequently develop secondary tuberculosis.
- Because of the preexistence of hypersensitivity, the bacilli excite a marked tissue response around the focus.
- As a result of this localization, the regional lymph nodes are less prominently involved than in primary tuberculosis.
- On the other hand, cavitation occurs readily in the secondary form resulting in dissemination along the airways.

Gross:

- The lesion is localized to the apex of one or both upper lobes. This may be related to high oxygen tension in the apices. apical scar (healed)
- The initial lesion usually a small focus of consolidation, less than 2 cm in diameter, within 1 to 2 cm of the apical pleura. Such foci are sharply circumscribed, firm, gray-white to yellow areas. caseation
- In favorable cases, progressive fibrous encapsulation occurs, leaving only fibrotic scars. fibrotic scars

Microscopic:

- The active lesions show characteristic coalescent tubercles with caseation (Fig 2.118).
- Although tubercle bacilli can be demonstrated by appropriate methods in early lesions, it is usually impossible to find them in the late fibrotic stages.

Fate:

Localized apical, secondary pulmonary TB may heal with fibrosis either spontaneously or after therapy, or the disease may progress.

Progressive Pulmonary Tuberculosis:

- The apical lesion enlarges with expansion of the area of caseation.
- Erosion into a bronchus evacuates the caseous center, creating a ragged, irregular cavity lined by caseous material that is poorly walled off by fibrous tissue.
- Erosion of blood vessels results in hemoptysis.
- With adequate treatment, healing by fibrosis occurs. Irregular cavities free of caseation necrosis may remain in the surrounding fibrosis.
- If the treatment is inadequate, or if host defenses are impaired, the infection may spread by direct expansion, via dissemination through airways, lymphatic channels, or the vascular system.

Complications (Fig. 2.19):

- 1- Pleural complications as TB effusions, TB empyema, or obliterative fibrous pleuritis.
- 2- Endobronchial, tracheal and laryngeal TB may develop.
- 3- Miliary pulmonary disease:-
 - This occurs when organisms drain through lymphatics, which empty into the venous return to the right side of the heart and then into the pulmonary arteries.
 - Individual lesions are either microscopic or small, visible (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma.
 - Miliary lesions may expand and coalesce to yield almost total consolidation of large regions or even whole lobes of the lung.
- 4- Systemic miliary tuberculosis:
 - It ensues when infective foci in the lungs seed the pulmonary venous return to the heart; the organisms subsequently disseminate through the systemic arterial system.
 - Almost every organ in the body may be seeded. It is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis.
 - Lesions resemble those in the lung.

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5. Isolated-organ tuberculosis:

- These may appear in **any organ** seeded hematogenously and may be the **presenting manifestation** of tuberculosis.
- Organs typically involved include the **meninges, kidneys, adrenals** (formerly an important cause of Addison disease), **bones, and fallopian tubes.**

6. Amyloidosis may appear in persistent cases.

Clinical features of secondary TB:

- Localized secondary tuberculosis may be **asymptomatic**.
- Systemic symptoms: often appear **fever and night sweating**. They are related to cytokines release (e.g., **malaise, anorexia, weight loss, low TNF and IL-1**).
- Progressive pulmonary TB with cavitation manifest as **productive cough with bloody sputum. Pleuritic pain** may result from extension of the infection to the pleural surfaces.
- Extrapulmonary manifestations of tuberculosis depend on the organ system involved (e.g., **TB salpingitis may present as infertility, TB meningitis with headache and neurologic deficits and Pott's disease with paraplegia**).

The diagnosis of pulmonary TB is based on:

- **History, physical and radiographic findings of consolidation, cavitation in the apices of the lungs.**
- **The most common method for diagnosis of TB remains demonstration of acid-fast organisms in sputum by acid-fast.**
- **Culture and PCR.**

Prognosis of tuberculosis:

- It is generally favorable if infections are localized to the lungs.
- It worsens significantly when the disease occurs in **aged, debilitated, immune-suppressed persons, who are at high risk for development of military TB.**

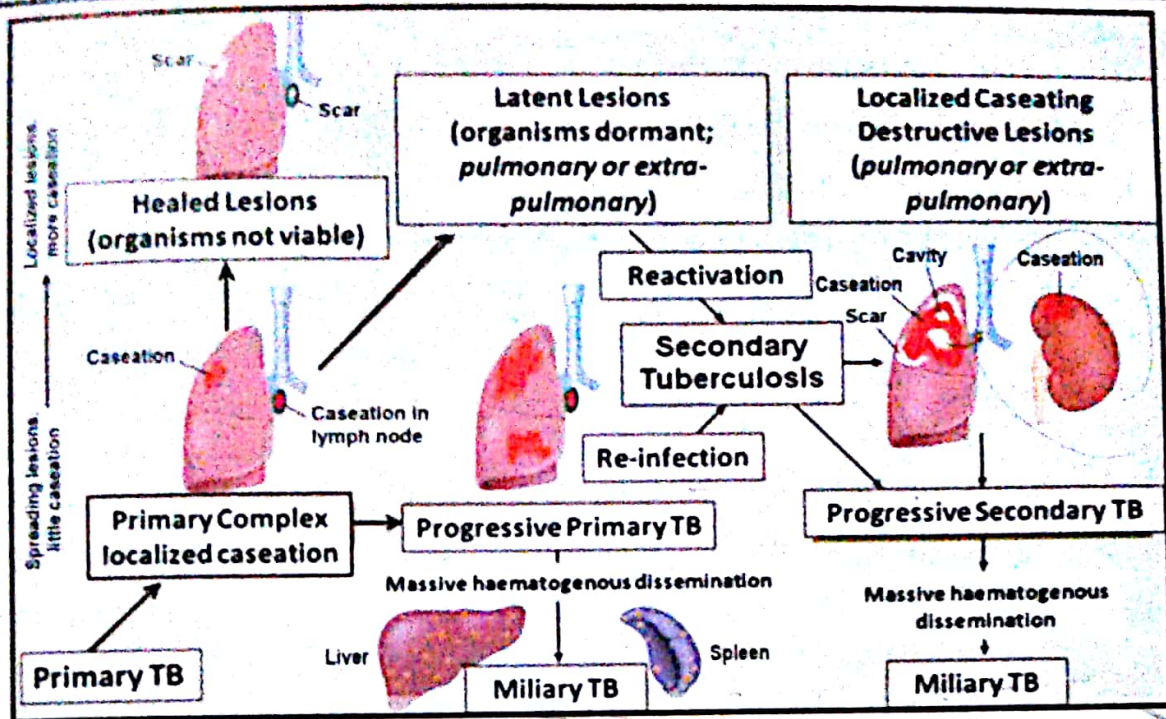


Fig.2.19: Complications of secondary pulmonary tuberculosis

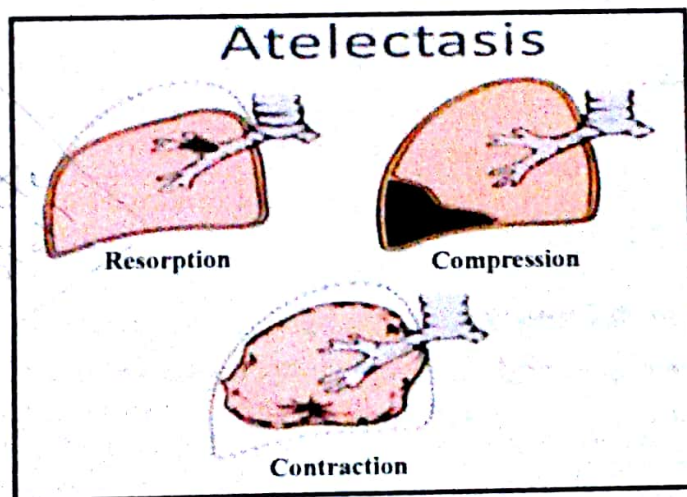


Fig.2.20: Types of lung collapse

Pulmonary collapse (Atelectasis)

It is loss of lung volume caused by inadequate expansion of airspaces.

It results in shunting of inadequately oxygenated blood from pulmonary arteries into veins, giving rise to a ventilation-perfusion imbalance and hypoxia.

Aetiological Types (Fig.2.20):

(I) Pressure collapse (compression collapse)

It is failure of expansion due to pressure on the lung from outside i.e. mechanical compression on lung by fluid, air or blood in pleural cavity or mediastinum.

Causes:

1. Pleural effusion
2. Haemothorax
3. Empyema leads to massive collapse.
4. Pneumothorax
5. Mediastinal causes e.g. tumour, aneurysm ... etc.

N.B. In this collapse the reduction in lung volume is pronounced.

(II) Absorption collapse (obstruction)

It is obstruction of bronchi or bronchioles with subsequent resorption of the air in the corresponding area of lung tissue.

Causes:

1. Acute complete obstruction of large bronchus as in:
 - Inhaled foreign body and mucus collection.
 - In terminal illness after tracheostomy, and after lung infection.
 - Postoperative due to combined effect of tenacious mucus, poor respiratory movement and depressed cough reflex.
2. Chronic bronchial obstruction as in:
 - Tumours growing in the wall of a bronchus.
 - Pressure on the wall of bronchus from outside e.g. aneurysm, enlarged lymph node or tumour.

N.B.: In this collapse the lung does not change much in size.

(III) Contraction collapse:

Occurs when either local or generalized fibrotic changes in the lung or pleura hamper expansion and increase elastic recoil during expiration

Appearance of collapsed lung:

Gross

- Pleural surfaces are wrinkled.
- Cut surface is airless, rubbery and bluish red (unoxxygenated blood)

Microscopic: Alveoli are collapsed (slit-like) and pulmonary arterioles are constricted. Prolonged cases show proliferation of granular pneumocyte associated with progressive pulmonary fibrosis

Congenital Atelectasis: It is failure of the lung to expand properly at birth. the alveoli have never been expanded.

Causes include prematurity and hyaline membrane disease.

Pneumoconiosis

It denotes the non-neoplastic lung reaction to inhalation of mineral dust.

Mineral dust pneumoconiosis includes exposure in workplace to coal (coal worker pneumoconiosis "CWP"), silica and asbestosis (Table.2.1).

The lung reaction depends on:

1- Size of inhaled particles;

- Large particles >5-10 microns will not reach distal airspaces.
- Intermediate particles 1-5 microns will be entrapped at the distal airspaces.
- Small particles 0.5 microns will diffuse as gas through airspaces.

2- Reactivity

- Coal dust is relatively inert large amounts must be deposited in the lungs before lung disease is clinically detected.
- Silica and asbestos are more reactive resulting in fibrotic nodules at lower concentrations.

Table.2.1: Mineral dust-induced lung diseases.

Agent	Disease	Exposure
Coal (CWP)	♦ <u>Asymptomatic anthracosis</u> ♦ <u>Simple coal worker pneumoconiosis</u>; Occurs in upper lobes and in upper zones of lower lobes. Macules & nodules (dust-laden macrophages & little Collagen) no pulmonary dysfunction ♦ <u>Complicated coal worker pneumoconiosis</u>; - PMF (pulmonary massive fibrosis-cor pulmonale) - Caplan syndrome (rheumatoid arthritis & pneumoconiosis)	Coal mining
Silica	♦ <u>Acute silicosis</u> (interstitial inflammation) ♦ <u>Chronic silicosis</u> (fibrotic nodules) ♦ <u>PMF</u>	Sandblasting, stone cutting, ceramics
Asbestos	♦ <u>Asbestosis</u> with interstitial fibrosis ♦ <u>Localized fibrous plaque</u> or <u>diffuse pleural fibrosis</u> ♦ <u>Pleural effusions</u> ♦ <u>Bronchogenic carcinoma</u> ♦ <u>Mesothelioma</u>	Mining, milling & fabrication of ores, shipyards, insulators
Byrrliosis	♦ <u>Type IV hypersensitivity reaction, pulmonary granulomas and fibrosis.</u>	Aerospace industry

NR:

- **COPD:** No increased frequency of TB or bronchogenic carcinoma. Once pulmonary fibrosis develops, it may become progressive even if further exposure to dust is prevented.
- **Silicosis:** Increased frequency of TB and carcinogenesis.
- **Asbestos:** Risk of cancer lung is increased 5 folds, and more with concomitant cigarette smoking. Increased risk for mesothelioma.

Acute Respiratory Distress Syndrome (ARDS):

ARDS is a clinical syndrome caused by diffuse alveolar capillary and epithelial damage with rapid onset of:

- Life-threatening respiratory insufficiency.
- Cyanosis.
- Severe arterial hypoxemia.
- May progress to multisystem organ failure.

Pathogenesis

- **Acute Phase:** In all conditions there is release of mediators by macrophages (IL-1, IL-8, IL-6 & TNF) leading to influx of activated neutrophils, interstitial edema, necrosis of capillary endothelial and alveolar epithelial cells.
- **Loss of surfactant** (due to damage of type 2 pneumocytes) results in hyaline membrane formation.

- Within 72 hours, DIC may become evident.

Patients who survive: there is release of mediators TGF & PDGF causing fibrosis.

Microscopic: Alveolar oedema, epithelial necrosis, accumulation of neutrophils and presence of hyaline membrane lining the alveolar ducts.

Tumours of the lung

Lungs are frequently the site of metastases from cancers of extra thoracic organs; however primary lung cancer is currently the most frequent diagnosed major cancer in the world and the most common cause of mortality worldwide.

Primary Lung Tumours:

- **Bronchogenic carcinoma (95%)** arise from the bronchial epithelium.
- The remaining 5% include:

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- **Bronchial carcinoid.**
- Bronchial gland tumours (e.g., adenoid cystic and **mucoepidermoid carcinoma**), mesenchymal malignancies (e.g. **fibrosarcoma** and **leiomyosarcoma**).
- **Lymphoma.**
- Benign lesions (e.g. **hamartoma**, **squamous-cell papilloma**, **angioma**, **fibroma**, **chondroma**, **lipoma**, and **leiomyoma**).

Bronchogenic carcinoma:

- Bronchogenic carcinoma ranks first among causes of cancer related deaths in **males in industrialized countries**.
- It becomes the leading cause of cancer deaths in **women** as well (due to **increase of smoking among female**).
- Sex incidence; Male to female ratio has changed from **2:1 to 1.5:1**.
- The peak incidence is between ages **50-60 years**.
- At time of diagnosis more than 50% of patients have distant metastases, while 25% have regional lymph nodal metastases.

Etiology and Pathogenesis:

I- Tobacco smoking: There is a positive linear relationship between tobacco smoking and lung cancer.

- **Average smokers have 10 fold risk**, while **heavy smokers** (>40 cigarettes/day for several years), have a **60 fold greater risk** than non smoker. Potential carcinogens in cigarette smokes include **polycyclic aromatic hydrocarbon** e.g. **benzopyrene**.
- Cigar and pipe smoking increase the risk, but much less than smoking unfiltered cigarettes.

II. Industrial hazards which increase risk of lung cancer:

1. All types of **radiation**.
2. **Asbestos**: Exposure to asbestos **increases the risk is 5 times in nonsmokers and 55 times in heavy smokers**.
3. Nickel, chromium, coal, mustard gas, arsenic and **vinyl chloride**.

III. Air pollution: plays a role in increasing the incidence of lung cancer.

IV. Genetic factors (Fig.2.21):

- **Inactivation of P53 and P16** suppressor genes.
- **Activating mutations of EGFR and k-ras oncogene** (especially in **adenocarcinoma**).

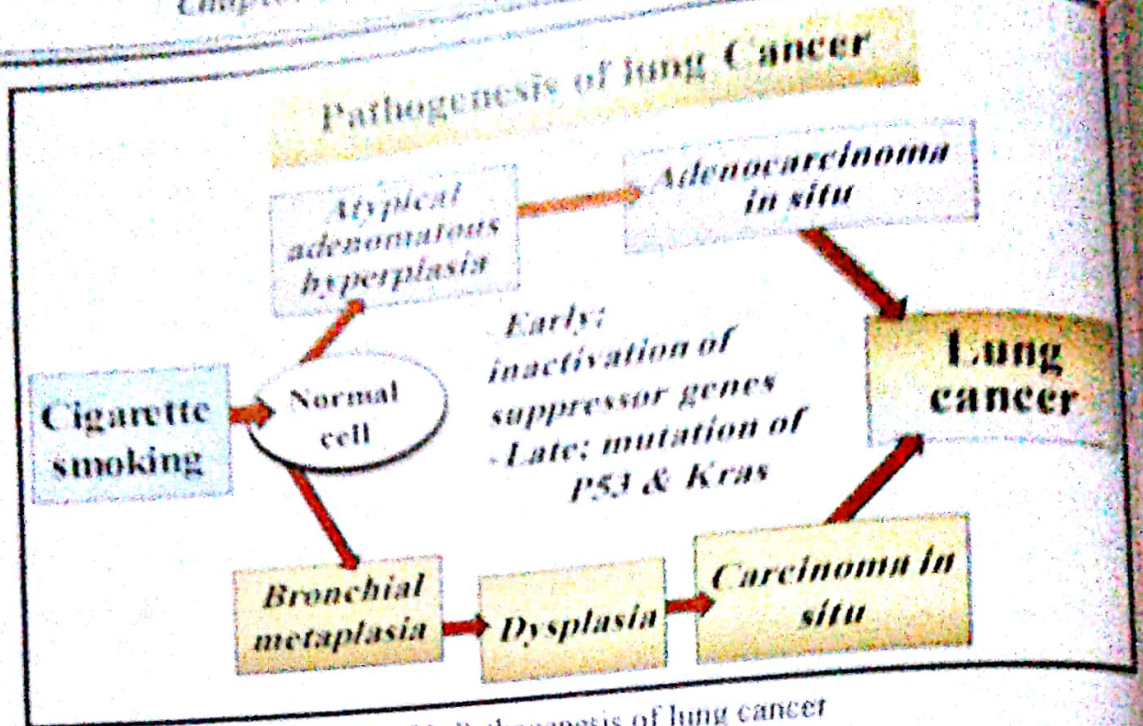


Fig.2.21: Pathogenesis of lung cancer

For therapeutic purposes bronchogenic carcinoma is classified into broad groups:

- 1- Small cell lung cancer (SCLC)
- 2- Non small cell lung cancer (NSCLC) including squamous carcinoma, adenocarcinoma, and large cell carcinoma.

The key reason for this distinction is that:

- All SCLCs have metastasized by the time of diagnosis and hence are not amenable to curative surgery. They are best treated by chemotherapy with or without radiation.
- In contrast to NSCLCs which usually respond poorly to chemotherapy and are better treated by surgery.

Pathological features of bronchogenic carcinoma:

Site: Arises mostly in and around the hilus of the lung.

Some arise in the periphery of the lung (including adenocarcinoma).

Gross: Bronchogenic carcinoma appears as a firm mass having greyish surface with areas of hemorrhage and necrosis.

- It begins as a small firm greyish mucosal lesion.
- It may grow as intraluminal mass, invades the bronchial wall or form large bulky mass pushing the adjacent lung tissue.
- Finally it may extend to the pleura.
- It may spread to the hilar lymph nodes.

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Microscopic types of bronchogenic carcinoma:

(1) Squamous cell carcinoma: Incidence: 35-50%

- Most common in males.
- Central and closely related to smoking (Fig. 2.22).
- Rapid rate of local growth metastasizes later.
- Large lesions may undergo central necrosis giving rise to cavitation.

Microscopic: Invasive squamous cell carcinoma of various grades of differentiation (Fig. 2.23).

NB: Squamous cell carcinoma is usually preceded by:

squamous metaplasia or dysplasia, which transforms into carcinoma in situ of the bronchial epithelium, a phase that may last for several years.

(2) Adenocarcinoma: Incidence: 15-35%

- Recently, it becomes the most common primary lung tumour in US.
- It is most common type in females and nonsmokers, although it is also common in smokers.
- Slow rate of growth, but tends to metastasize early.
- It is usually peripherally located (Fig. 2.24), but may be central.
- The precursor of peripheral adenocarcinomas has been described as atypical adenomatous hyperplasia (AAH). It is a well-demarcated focus of epithelial proliferation of low-columnar cells which demonstrate various degrees of cytologic atypia.

Microscopic:

- Acinar (well differentiated, with gland formation).
- Papillary.
- Solid masses.

Adenocarcinoma in situ:

- Formerly called bronchiolo-alveolar carcinoma.
- It occurs in the peripheral portion of the lung as single nodule, 3cm or less in diameter.
- **Microscopic:** composed of tall columnar to cuboidal, non-mucin or mucin-secreting epithelial cells that grow in a monolayer along the alveolar septa, no stromal invasion and no desmoplasia (Fig. 2.25).

NB: Adenocarcinoma may arise through; An atypical alveolar adenomatous hyperplasia ➤ adenocarcinoma in situ ➤ invasive adenocarcinoma sequence.



Fig.2.22: Central squamous CC



Fig.2.23: Squamous CC Grade II



Fig.2.24: Peripheral lung adenocarcinoma

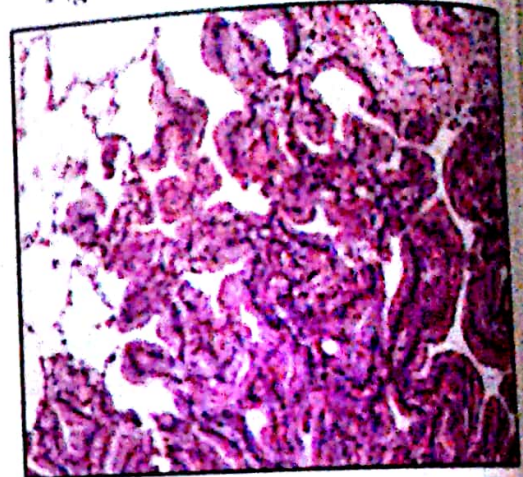


Fig.2.25: Adenocarcinoma in situ

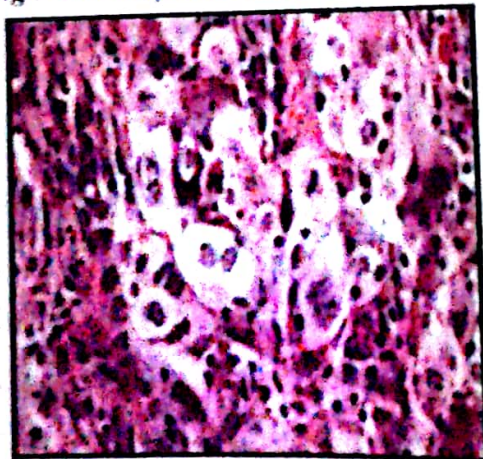
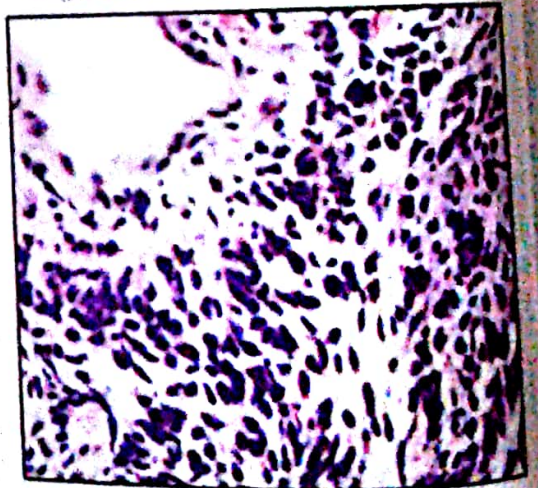


Fig.2.26: Large cell lung carcinoma



(3) Large cell carcinoma. Incidence: 10 -15%

- ♦ Cancer cells are **large**, with **excess cytoplasm**, **large nuclei** and **conspicuous nucleoli** (Fig.2.26).
- ♦ They probably represent cases of squamous cell carcinoma and adenocarcinomas that are so undifferentiated and can no longer be recognized.

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(4) Small cell carcinoma - Incidence: 20 - 25%

- Highly malignant tumour, it is the most aggressive.
- Has a strong relationship to cigarette smoking.
- Mostly hilar and central.
- Grows quickly and metastasize early.
- Sixty to seventy percent have metastatic disease at presentation.
- Incurable by surgery.

Microscopic:

- Sheets of small round or fusiform cells with scant cytoplasm and finely granular chromatin. Mitotic figures are frequent and necrosis may be extensive (Fig. 2.27).
- Neurosecretory granules (vesicles containing neuroendocrine hormones) are seen by EM, in some of these tumour cells which give this tumor an endocrine / paraneoplastic syndrome association.

Incidence of different types of bronchogenic carcinoma: (Fig. 2.28)

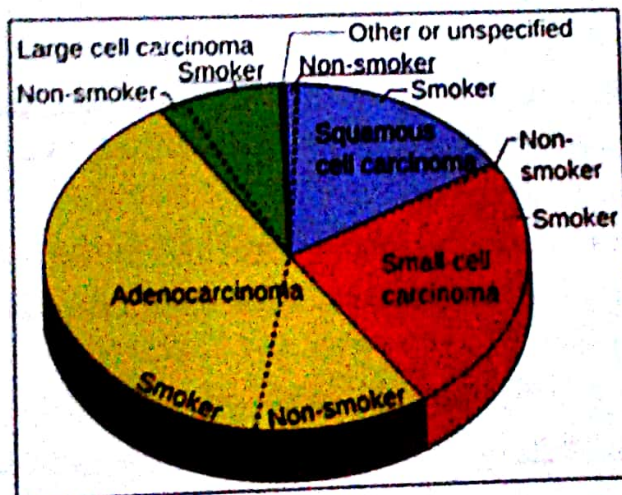


Fig. 2.28: Incidence of different types of bronchogenic carcinoma and their relation to smoking

Spread of bronchogenic carcinoma:

A- Local spread:

1. Bronchial: lumen obstruction causes pulmonary collapse, accumulation of secretions, ulcerative bronchitis, bronchiectasis, abscess or pneumonia.
2. Pleural: blood-stained effusion, empyema, chest wall invasion.
3. Superior vena cava: compression or invasion causes superior vena caval syndrome.
4. Pericardium: pericarditis with haemorrhagic effusion.

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5. Bone involvement: direct spread into ribs, sternum and spine result in pain, hypercalcaemia and pathological fracture.
6. Oesophagus: causing dysphagia or bronco-oesophageal fistula.
7. Nerves: Pancoast tumour, with invasion of the brachial plexus, or cervical sympathetic chain leading to Horner's syndrome.

B- Lymphatic Spread:

It occurs early with invasion of regional intrapulmonary, hilar and then extrapulmonary tracheobronchial and other mediastinal nodes. Further spread may occur to cervical, supraclavicular, axillary and more distant groups.

C- Blood Spread:

Wide spread systemic invasion is common and metastases may be the first manifestation of an occult bronchogenic carcinoma. No organ is spared.

Favourite sites of metastasis:

- Adrenals: are involved in over 1/2 of cases (50%)
- Liver: involved in 30 - 50 % of cases.
- Brain: involved in 20%: The special tendency to brain metastases may overshadow the primary bronchial tumor clinically.
- Bone: involved in 20%. Thoracic vertebrae are frequently involved possibly by retrograde venous route.

Clinical features:

- Bronchogenic carcinoma is usually silent and insidious.
- Chronic cough and expectoration may call attention to still localized resectable tumour.
- Paraneoplastic syndrome in 3%-10% of all lung cancer patients.
 1. Hypercalcaemia due to release of parathyroid like hormone (most commonly with squamous cell carcinoma).
 2. Cushing syndrome due to release of adrenocorticotrophic hormone.
 3. Hyponatremia and water retention.
 4. Neuromuscular syndrome including myasthenic syndrome, peripheral neuropathy and polymyositis.
 5. Clubbing of fingers
 6. Migratory thrombophlebitis, specially with adenocarcinoma.
- Superior vena caval syndrome
- Pancoast's tumours:
 - They are apical lung cancers that tend to invade neural structures around the trachea, including the cervical sympathetic plexus.

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Clinically; invasion of brachial plexus manifests as pain along the distribution of the ulnar nerve while invasion of the sympathetic chain leads to development of Horner's syndrome (enophthalmos, meiosis, ptosis, and anhidrosis)

Bronchial carcinoid:

- Malignant tumours, represent about 5% of all lung tumors.
- Occurs at an early age, with a mean of 40 years.
- Sex incidence; equal.
- No known relationship to cigarette smoking or other environmental factors.

Gross:

- The tumors grow as spherical polypoid masses (3 to 4 cm), project into the lumen of the main bronchus, covered by intact mucosa (Fig. 2.29a).
- Some tumors produce little intraluminal mass, and then penetrate the bronchial wall to fan out in the peribronchial tissue producing the collar-button lesion.

Microscopic:

- Typical carcinoid (low grade): composed of nests, cords and masses of regular cells with uniform round nuclei, separated by a delicate fibrous stroma. Mitoses are rare (Fig. 2.29b).
- Atypical carcinoid (intermediate grade): cells display a higher mitotic rate and focal necrosis. They have a higher incidence of nodal and distant metastasis compared to typical carcinoids.
- E.M. shows neurosecretory granules in their cytoplasm.

Clinical features:

- 1- May be asymptomatic (especially in peripheral carcinoids).
- 2- Bronchial obstruction, with cough, repeated infection, hemoptysis.
- 3- Rarely carcinoid syndrome (intermittent attacks of diarrhea, flushing and cyanosis).
- 4- Distant metastases are rare.

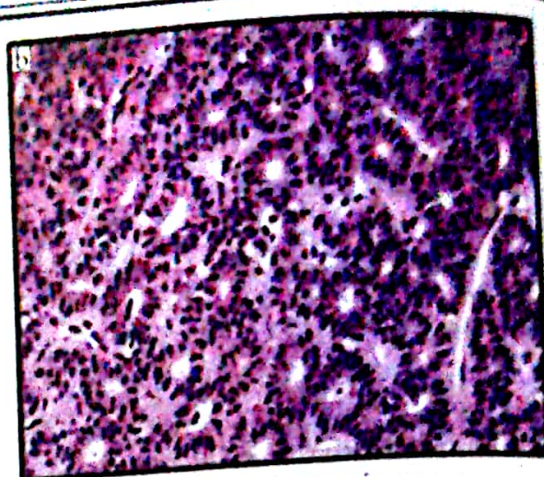


Fig.2.29: Bronchial carcinoid, (a) gross,

(b) microscopic

Metastatic tumours of the lung:

- Are **more common than benign tumors**.
- Both carcinomas and sarcomas arising anywhere in the body may spread to the lung via blood or lymphatics or by direct continuity e.g. with oesophageal carcinomas and mediastinal lymphomas.

Patterns of metastatic growth:

- **Multiple, discrete nodules scattered throughout all lobes**, particularly in the periphery.
- **Cannon-Ball metastases** are confined to **blood-borne, large metastatic nodules, originating from renal cell carcinoma or testicular tumours**.
- When the tumor has extended to the lung through lymphatics, the growths confine themselves to peribronchial and perivascular tissue spaces.

Diseases of the pleura

I- Inflammations of the pleura:

(1) Serofibrinous pleuritis:

Causes:

1. Inflammatory diseases within the lung e.g. T.B., pneumonia, lung infarcts, lung abscess, bronchiectasis.
2. Rheumatoid arthritis and disseminated lupus erythematosus.
3. Uraemia
4. Irradiation used in therapy of tumors in the lung or mediastinum.

Fate: Resolution or organization (less common)

(2) Suppurative pleuritis (empyema):

Causes:

1. Contagious spread of organisms from pulmonary suppuration; e.g. lung abscess, bronchiectasisetc.

Chapter 2: Diseases of the respiratory system

2. Lymphatic or haematogenous dissemination from distant infection.
3. Suppurative infection below the diaphragm e.g. subdiaphragmatic abscess or liver abscess.

Fate:

- Resolution (less common).
- Organization of the exudate, with formation of dense, tough, fibrous adhesions that obliterate the pleural space.

Complications:

1. Toxaemia: systemic effects of infection are marked.
2. Lung collapse: compression of the lung with impaired lung function.
3. Bronchopleural fistula: infection ruptures into the airways and pleura resulting in fistulous communication.

(3) Haemorrhagic pleuritis:

True sanguinous inflammatory exudate is caused by:

- Haemorrhagic diathesis.
- Tuberculosis.
- Rickettsial diseases.
- Neoplastic involvement.

II Non inflammatory pleural effusions:

(1) Hydrothorax:

It is non inflammatory collections of serous fluid within the pleural cavity.

Causes:

1. Cardiac failure.
2. Renal failure.
3. Cirrhosis of liver.

Effects:

- Causes compression & collapse of the underlying lung tissue.
- If the cause is removed, hydrothorax may be resorbed without permanent alterations.

(2) Haemothorax:

It is accumulation of blood in the pleural cavity.

Causes: A fatal complication of a ruptured aortic aneurysm.

Effects:

- Being fatal, it leads to death within minutes or hours, with no response within pleural cavity.
- Rarely, leakage of smaller amounts of blood is not fatal, become organized with pleural adhesions.

(3) Chylothorax:

It is accumulation of milky fluid lymphatic origin, in the pleural cavity.

Causes: 1. Malignancy within the thoracic cavity e.g. malignant lymphoma causing obstruction of the major lymphatic ducts.
2. Distant cancers may metastasize via lymphatics and grow within the right lymphatic or thoracic duct leading to obstruction. Obstruction causes rupture of these ducts and escape of milky-white chylous fluid.

Pneumothorax:

It denotes the presence of air or gas in the pleural cavity

Types of pneumothorax:

1- Spontaneous pneumothorax

a- Idiopathic spontaneous pneumothorax

In young, healthy adults due to rupture of small peripheral subpleural blebs (paraseptal=distal emphysema)

b- Idiopathic secondary pneumothorax

Lung lesions as TB, lung abscess, carcinoma, emphysema and asthma

2- Traumatic pneumothorax

By perforating injuries to the chest wall, but sometimes the trauma pierces the lung giving two ways for the accumulation of air in the pleural space

NB: Tension Pneumothorax: It is a life-threatening condition, caused by ball and valve leak that may occur as a result of trauma, lung infection, or during mechanical ventilation or resuscitation. The air enters the pleura during inspiration and cannot get outside during expiration leading to progressive accumulation of air impairing the pulmonary circulation.

Tumors of the Pleura:

Malignant mesothelioma:

- Are rare tumors, arises from either the visceral or parietal pleura.
- Its incidence increased in the past few years among persons with heavy exposure to asbestos after a long latent period of 25-45 years.

Gross:

- The affected lung is ensheathed by a thick layer of soft, gelatinous, reddish pink tumor tissue.
- Associated with extensive pleural effusion and direct invasion of thoracic structures.

Microscopic:

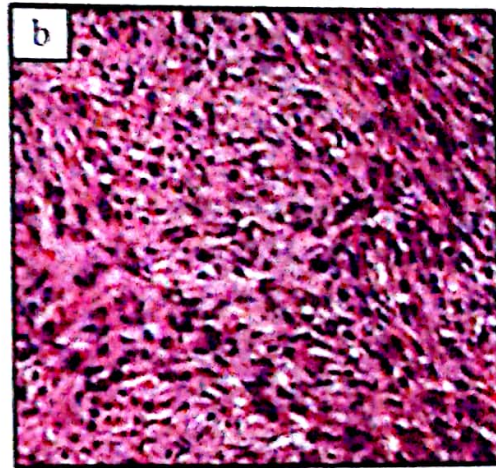
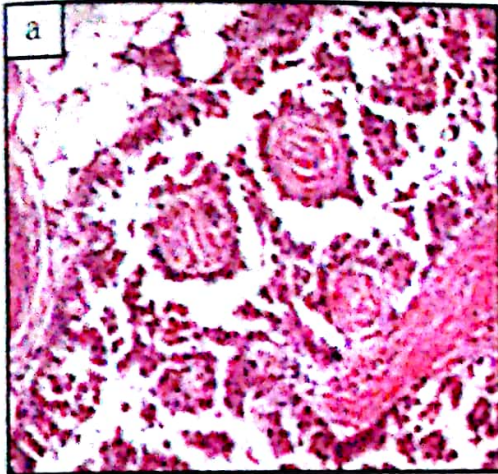
a- Epithelial type (papillary):

Cuboidal or columnar or flattened cells, forming tubular and papillary structures (Fig.2.30a).

b- Sarcomatoid type: (mesenchymal)

Appears as spindle-cell sarcoma or fibrosarcoma (Fig.2.30b).

c- Mixed epithelial and sarcomatous type.



Secondary Tumours of the Pleura:

- More common
- They may arise from
 1. Primary neoplasm of lung.
 2. Primary neoplasm of breast; directly, via lymphatic or blood.
 3. Ovarian carcinoma.

N.B. Serous or serosanguinous effusions follow metastatic involvement, which contain **desquamated neoplastic cells**.

Haemoptysis:

Hemoptysis means coughing blood.

It occurs in a variety of clinical lung conditions including:

1. Chronic venous congestion in mitral stenosis and left sided heart failure due to rupture of pulmonary capillaries under increased hydrostatic pressure.
2. Pulmonary tuberculosis.
3. Pulmonary infarction.
4. Inflammation of the lung as bronchitis and pneumonia.
5. Suppurative lung diseases such as bronchiectasis, lung abscess gangrene.
6. Lung carcinoma.
7. Haemorrhagic blood diseases: as purpura and leukemia.

SUMMARY

Diseases of the nose:

Rhinitis means inflammation of the mucous membrane of the nose.

Epistaxis: It is bleeding from the nose.

Tumours of the nose are rare.

Diseases of the tonsils:

Tonsillitis: It is inflammation of the tonsils.

Diphtheria; It is a membranous inflammation in the upper respiratory tract (rarely in the upper gastrointestinal tract) with toxemia.

Diseases of the larynx:

Laryngitis, laryngeal polyp (Nodule).

Tumors include; *squamous cell papilloma and carcinoma* of the larynx.

Diseases of the lungs:

1- Obstructive: Emphysema, chronic bronchitis & bronchial asthma.

2-Restrictive Diseases: acute respiratory distress syndrome, pneumoconiosis, sarcoidosis and idiopathic pulmonary fibrosis.

Bronchiectasis: Permanent dilatation of bronchi and bronchioles caused by destruction of the muscle and the supporting elastic tissue resulting from or associated with chronic necrotizing infections

Pneumonia:

- **Bacterial pneumonia:** Bronchopneumonia and lobar pneumonia

- **Primary atypical Pneumonia:** Mycoplasma pneumonia, viruses

Lung abscess: Aspiration, postpneumonic, pyaemic and miscellaneous.

Suppurative lung diseases include: Bacterial pneumonia, lung abscess, empyema, gangrene and bronchiectasis.

Pulmonary Tuberculosis; Primary and secondary TB.

Pulmonary atelectasis: Pressure; absorption and contraction collapse.

Pneumoconiosis; coal worker pneumoconiosis, silica and asbestosis.

Acute Respiratory Distress Syndrome (ARDS); is a progressive respiratory insufficiency caused by diffuse alveolar capillary and epithelial damage.

Tumours of the lung:

1-Bronchogenic carcinoma (95% of primary lung tumours)

Types: SCLC & NSCLC; adeno, squamous and large cell carcinoma.

Precursors include; squamous dysplasia and atypical adenomatous hyperplasia and carcinoma in situ.

Bronchial carcinoid; 5% of lung tumours. Histologically typical & atypical.

Diseases of the pleura:

I- **Pleuritis;** serofibrinous, suppurative and haemorrhagic.

II- **Non inflammatory;** hydrothorax, haemothorax and chylothorax.

Pneumothorax; Types: Idiopathic and traumatic pneumothorax

Malignant mesothelioma; Sarcomatoid, epithelial and mixed types.

Chapter 3

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- ❑ Define lymphadenitis, mention its types, causes, describe its pathologic features and list its complications.
- ❑ Identify Hodgkin's lymphoma compare and contrast between variants of Hodgkin's lymphoma.
- ❑ Classify Non Hodgkin lymphoma and describe the clinical and pathologic features of each type.
- ❑ Analyze and diagnose a pathologic condition based on given clinical, radiologic data and / or laboratory findings.
- ❑ Identify types and causes of hypersplenism.
- ❑ Define congestive splenomegaly and list its causes and describe its pathologic features.
- ❑ Define thymoma, mention its types and biological behavior.
- ❑ Classify anaemias and describe the clinical, laboratory and pathologic features of each type.
- ❑ Define polycythemia and describe the clinical and pathologic features of each type.
- ❑ Compare and contrast between chronic lymphatic and chronic myeloid leukemia.

don't be sad by
what see.
worry ends when
faith begins

Diseases of Lymph Nodes

Sites of lymphoid tissue:

The lymphoid tissue exists in bone marrow, thymus, lymph nodes, spleen, lymphoid tissue in the oropharynx, Peyer's patches of the terminal ileum and bronchus associated lymphoid tissue.

Normal anatomy:

The three major regions of a lymph node are: the cortex, paracortex and medulla (Fig. 3.1 & 3.2).

The cortex:

It is situated beneath the capsule and contains the lymphoid follicles which are formed of the following three zones from inside outwards:

- 1- Pale germinal center formed of:
 - Follicle center cells (B-lymphocytes) of two types; small centrocytes with cleaved nuclei and larger centroblasts with non-cleaved nuclei.
 - Macrophages engulfing cell debris in case of hyperplasia.
 - Dendritic cells.
- 2- Mantle zone: tightly packed mature small B-lymphocytes.
- 3- Marginal zone: less tightly packed mature B-lymphocytes present in hyperplastic lymphoid follicle.

NB: The B-lymphocytes are responsible for humoral immunity.

The paracortex:

It is the zone situated between the cortex and medulla, which contains T-lymphocytes, reticulum cells and immunoblasts (activated B or T lymphocytes) which have abundant eosinophilic cytoplasm and large vesicular nuclei with prominent eosinophilic nucleoli.

The medulla:

- It is close to the hilum and it is rich in lymphatic sinuses, arteries and veins.
- It contains only a minor lymphocytic component formed of mature B-lymphocytes, plasmacytoid lymphocytes and plasma cells migrating from the cortex and responsible for humoral immunity.

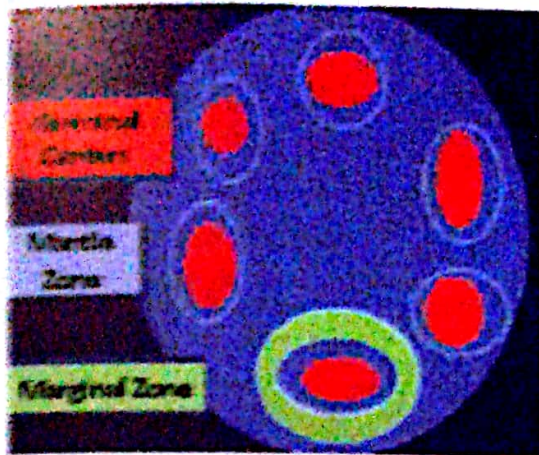


Fig.3.1: Normal lymph node micro-anatomy

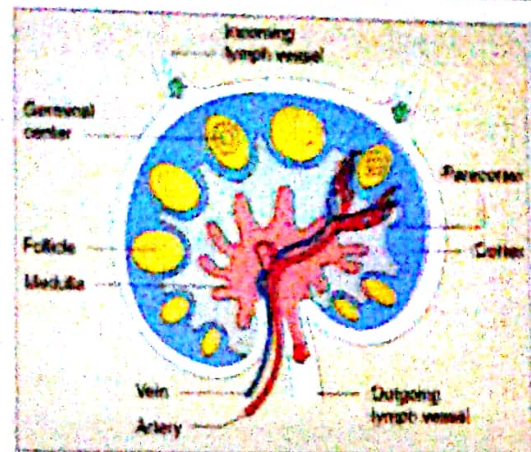


Fig.3.2: Zones of lymphoid follicle

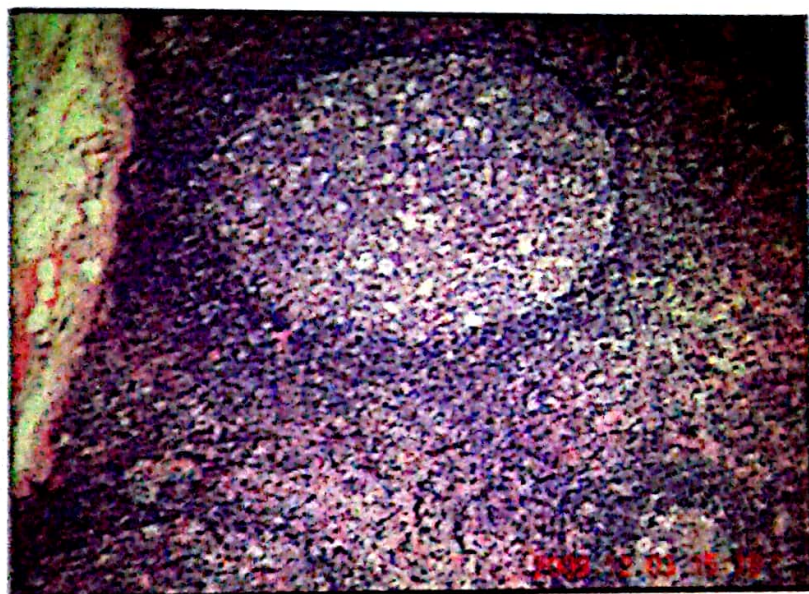


Fig.3.3: Reactive follicular hyperplasia

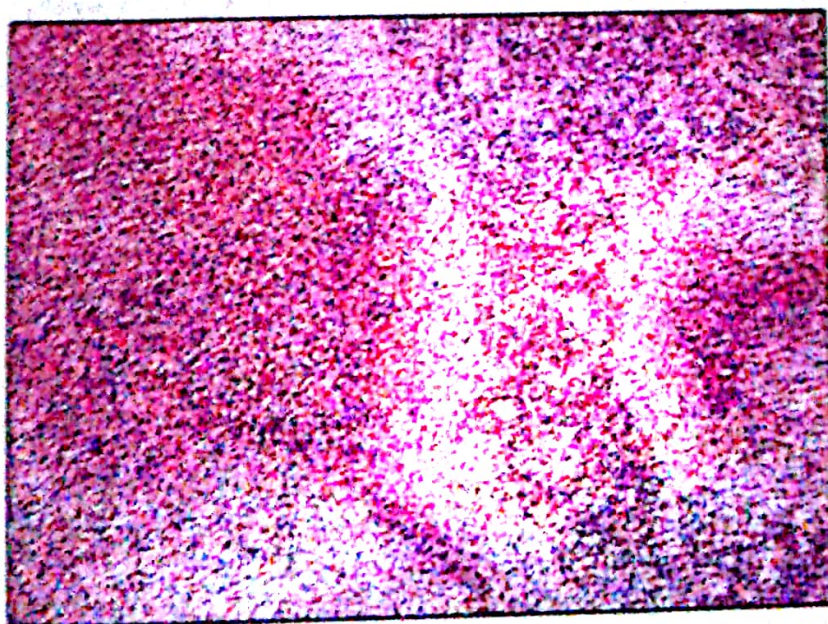


Fig.3.4: Cat scratch disease, with stellate necrotizing granulomas (arrows)

Inflammatory and hyperplastic diseases:

1. Acute non specific lymphadenitis:

- It usually occurs in lymph nodes draining acutely inflamed focus e.g. acute suppurative tonsillitis or abscess.
- It leads to nodal acute inflammatory reaction, rich in neutrophils.

Morphology: The lymph node is enlarged and tender and may be the seat of abscess formation.

2. Chronic non-specific lymphadenitis (reactive hyperplasia):

This condition assumes one of three patterns depending on the causative agent:

a- Reactive follicular hyperplasia:

The lymphoid follicles are prominent with enlargement of their germinal centers (Fig. 3.3).

It is associated with inflammatory processes that activate B cells as rheumatoid arthritis, toxoplasmosis and HIV.

b- Paracortical hyperplasia:

It is due to activation of the parafollicular T cells as in viral infection (EBV), follows vaccination or certain drugs (phenytoin).

c- Sinus histiocytosis:

The medullary sinuses are loaded with histiocytes. It is often encountered in nodes draining cancer (represent immune reaction to the tumor or its products).

3. Granulomatous lymphadenitis:

A- Tuberculosis:

Gross:

Early: The lymph nodes are enlarged, firm and not adherent together with grayish white cut surface.

Late lesions: The LNs become adherent to each other (matted together) due to periadenitis. The cut surface shows cheesy-like yellowish material (caseous necrosis).

Microscopic:

Early tuberculous lymphadenitis: There is infiltration by multiple small pale tubercles formed of aggregates of epithelioid cells, few Langhan's giant cells and minimal caseation.

Caseating tuberculous lymphadenitis: Most of nodal tissue is replaced by areas of caseous necrosis with multiple small tubercles at the periphery.

Complications and effects:

TB Cervical lymphadenitis:

- Cold abscess with multiple sinuses discharging caseous material
- TB of the skin around these sinuses.

TB mediastinal lymphadenitis:

- Pressure manifestation (mediastinal syndrome).
- Spread of infection to the lungs.

TB mesenteric lymphadenitis:

- Rupture of caseous lymph nodes leading to TB peritonitis.

NB: In addition, the following complications may occur in any type:

- Pathological calcification
- Hematogenous dissemination.
- Secondary amyloidosis.

B- Sarcoidosis: Non-caseating epithelioid granuloma.

C- Toxoplasmosis: Caused by *Toxoplasma gondii*
Non-caseating epithelioid cell microgranuloma
Diagnostic serological test: Toxoplasmin test.

D- Crohn's disease: Non-caseating epithelioid cell granuloma.

E- Cat-scratch disease:

It is thought to be caused by coccobacillary pleomorphic organism.

It is transmitted to man through skin scratches or bites of cats or rabbits.

Axillary group of lymph nodes are usually affected.

Microscopic: It is characterized by nodal formation of micro abscesses having central stellate shaped areas of necrosis with neutrophils surrounded by palisading of histiocytes i.e. stellate necrotizing granuloma (Fig. 3.4).

4. Infectious mononucleosis:-

It is a rare viral disease causing generalized lymphadenopathy, splenomegaly, mild fever and sore throat.

Microscopic: There is partial loss of nodal architecture with marked diffuse paracortical proliferation of atypical B-cell forms. This picture may be confused with malignant lymphoma.

Diagnosis:

- 1- Lymphocytosis with atypical lymphocytes in peripheral blood.
- 2- Positive heterophil reaction (monospot test).
- 3- A rising titer of specific EBV antibodies.

Tumours of lymphoid tissue

Tumours of lymph nodes are either primary or secondary:

1. Primary tumours: All are malignant and are called lymphomas. They may arise from nodal or extranodal lymphoid tissue.
2. Secondary tumours: These are the metastatic tumours which occur in lymph nodes draining a primary site of malignancy.

Lymphoma:

- ❑ They are primary malignant tumours of lymphoid tissue.
- ❑ They include tumours arising from T-or B-lymphocytes, histiocytes, monocytes and reticulum cells. The most common type is that of lymphocytic origin, particularly B-type.
- ❑ Lymphomas can be divided into two main categories:

A- Hodgkin lymphoma.

B- Non-Hodgkin lymphoma.

A- Hodgkin lymphoma

It is a tumor of B lymphocytes.

Gross: Lymph nodes are enlarged, firm (rubbery), discrete but may become adherent later on due to invasion of the capsule. The cut surface is homogenous grayish pink in colour.

Microscopic: It is characterized by the presence of malignant giant cells termed "Reed Sternberg cells" in a background of non-neoplastic small lymphocytes and a heterogenous population of benign inflammatory cells.

Reed Sternberg Cells (RSC):

- The classic RSC; is a large cell with abundant weakly eosinophilic cytoplasm. The nucleus is bilobed or polylobed with prominent nucleoli. In the most typical form; the diagnostic RS cells show two nuclei or nuclear lobes facing each other (mirror image). Each lobe contains a large acidophilic nucleolus surrounded by a clear zone giving an "owl eye" appearance (**Fig.3.5**).

- Atypical variants of RSC, include:

Popcorn variant lymphocytic predominant (LP) variant: The nucleus is puffy, multilobed with small punctuate nucleoli and scanty cytoplasm (**Fig.3.6**).

Lacunar variant: The nucleus is single to multilobed. The nucleolus is relatively small. The cytoplasm may retract and the cell appears to lie in a clear space or lacuna (**Fig.3.7**).

- Pleomorphic variant: The nucleus is single, irregular or multilobed. The nucleoli are variable in size (**Fig.3.8**).
- Mononuclear variant: This large cell contains one nucleus with large eosinophilic nucleolus. It may be seen in any subtype of Hodgkin's disease.

Immunohistochemistry, the classic RSC and its variants are positively stained by CD15 and CD30 antibodies which are diagnostic (**Fig.3.9**).

Classification of Hodgkin lymphoma (Microscopic Subtypes):

According to the frequency and type of RSC, predominant background cell type and occurrence of fibrosis, it is classified into (**Table.3.1**):

1. Nodular sclerosis type: most common

- The classic RSCs are very rare with increased number of lacunar variant. The background is formed of variable amounts of small lymphocytes as well as mixed inflammatory cells. These are divided into nodules by dense bands of fibrous tissue.
- This type has the best favourable prognosis.

2. Mixed cellularity type: 2nd most common

The classic RSCs are easily identified in a background of diffuse, mixed inflammatory cells including: Eosinophils, plasma cells, polymorphs, histiocytes as well as small lymphocytes.

3. Lymphocytic predominant type: 4th

The classic RSCs are rare with relative frequency of popcorn variant. The background is formed mainly of small resting lymphocytes in a diffuse pattern replacing the nodal architecture.

4. Lymphocytic depletion type: 3rd

- The classic RSCs are rare with occurrence of pleomorphic variant.
- The background is formed of few small lymphocytes as well as few mixed inflammatory cells.
- The infiltrate is diffuse and there is variable amount of fibrosis. This form of fibrosis may be predominant giving rise to a subtype of the disease called lymphocytic depletion with diffuse fibrosis.

Table 3.1: Classification of Hodgkin lymphoma:

Type	Histological Features	Frequency	Prognosis
Nodular sclerosis	Bands of fibrosis. Lacunar RSC	Most frequent type. Common in women	Best favorable, most are stage or II
Mixed cellularity	Composed of different cells. Classic RSC	Second most frequent. Most common in older persons.	Fair, most are stage III
Lymphocyte predominance	Many lymphocytes Popcorn RSC	Uncommon	Good, most are stage I or II
Lymphocyte depletion	Many Pleomorphic RSC	Uncommon	Poor, most are stage III or IV

Staging of Hodgkin lymphoma (Fig.3.10):

Stage I: Involvement of a single lymph node group (I) or involvement of a single extra-nodal organ or site (I_E).

Stage II: Involvement of two or more lymph node groups on the same side of the diaphragm alone (II) or with involvement of limited contiguous extra lymphatic organ or tissue (II_E).

Stage III: Involvement of lymph node group on both sides of diaphragm (III), which may include spleen (III_S) and/or limited contiguous extra lymphatic organ or site (III_{ES}, III_E).

Stage IV: Involvement of multiple or disseminated foci of one or more extra lymphatic organs or tissues with or without lymphatic involvement.

Clinical picture:

The disease occurs mainly in young and middle aged persons with a peak at the third decade and a male predominance. The patient may present by:

1. **Painless non tender enlarged lymph nodes.** *Pressure on the surrounding structure*
2. Mild intermittent fever, lasting for few days and followed by normal temperature for one or two weeks. This is called **Pel-Ebstein fever**.
3. Progressive anaemia. *cachexia → anaemia*
4. Loss of weight. *watery stools, mod*
5. Itching. *itching, redness, swelling, etc.*
6. Pressure manifestations caused by the enlarged lymph nodes

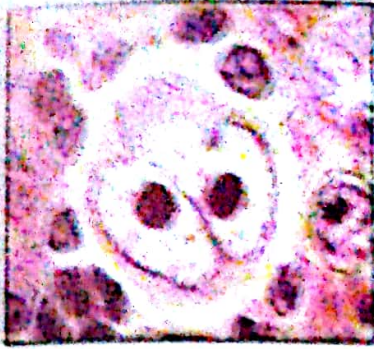


Fig. 3.5: Classic RSC

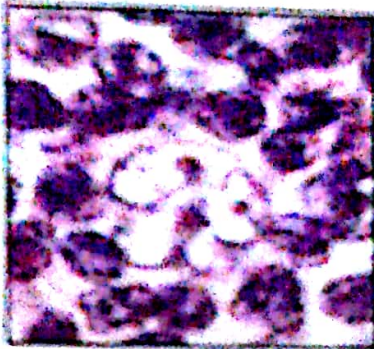


Fig. 3.6: Popcorn RSC

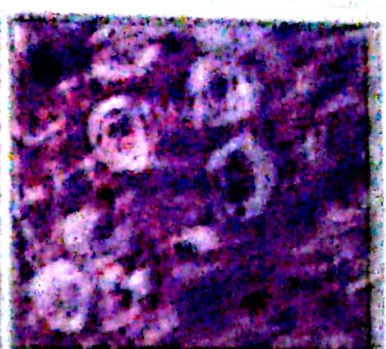


Fig. 3.7: Lacunar RSC

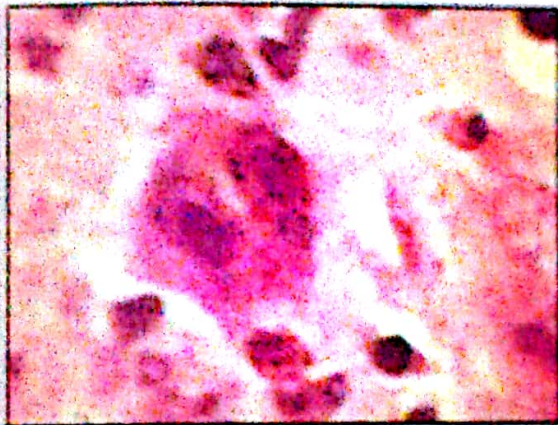


Fig. 3.8: Pleomorphic RSC

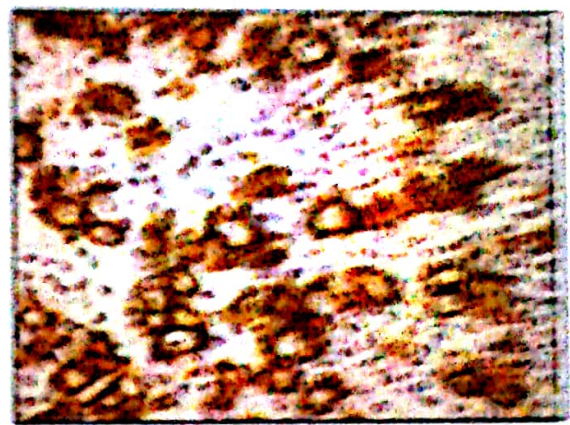


Fig. 3.9: RSC IHC stained for CD15

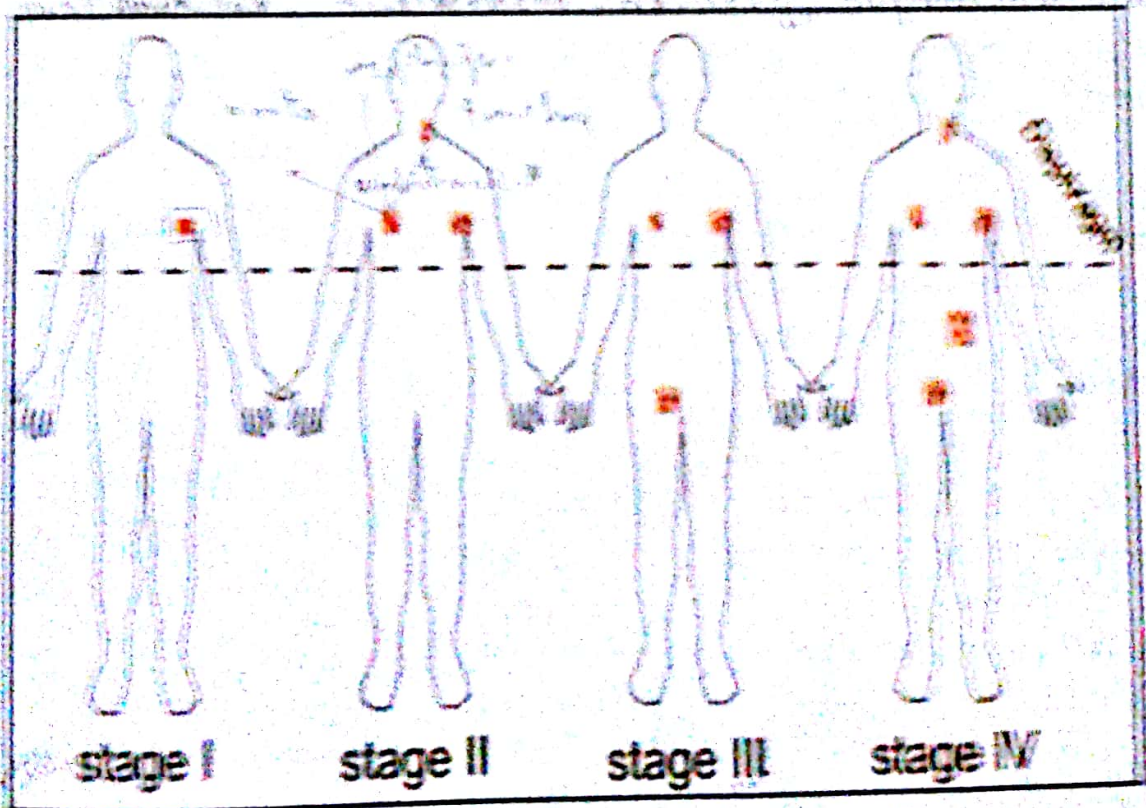


Fig. 3.10: Staging of lymphoma (Hodgkin & non-Hodgkin)

B- Non-Hodgkin lymphoma (NHL):

It is a diverse group of neoplastic disorders of lymphoid cells occurring at any stage of B or T-cell differentiation. It also may arise from nodal or extra nodal lymphoid tissue (Table.3.2).

Gross: The lymph nodes affected are enlarged, soft (commonly described as fish flesh) and pale grey in color. However, they may be firm if there is an associated fibrosis.

Microscopic: It is characterized by replacement of nodal architecture by neoplastic cell population which is monoclonal either of B or T-cell origin.

Immunohistochemistry, B-cells are positively stained by CD20 antibody while T-cells are positively stained by CD3 antibody.

Classification (microscopic subtypes):

Several classifications are applied to NHL. The most recently applied one is the WHO classification in 2008 (Table.3.3).

This classification relies mainly on the **type of cell origin**, its site (e.g. follicular center, mantle, paracortex or medulla) as well as its functional variety (e.g. B or T-cells).

Table.3.2: Origin of lymphoid neoplasms.

Central lymphoid tissue	Peripheral lymphoid tissue			
Precursor B & T-cells	Peripheral (mature) B-cell			Peripheral T-cell
Bone marrow (B) Thymus (T)	Mantle area	Follicular area	Marginal area	Paracortex
Precursor B/T cell lymphoblastic leukemia/ lymphoma • Multiple myeloma (B-cell)	Mantle zone lymphoma	Follicular lymphoma • Burkitt lymphoma • DLBCL • Hodgkin's Lymphoma	• DLBCL • Marginal zone lymphoma • Small lymphocytic lymphoma	• Peripheral T cell lymphoma

DLBCL - Diffuse large B-cell lymphoma

Table 3.3. WHO classification of selected types of non-Hodgkin lymphoma

B-cell lymphoma	T-cell lymphoma
B cell precursor - B-cell Leukemia/ lymphoma Mature B-cell Lymphomas - Follicular - Small lymphocytic - Lymphoplasmacytic - Marginal zone B-cell - Extranodal (MALT) - Nodal - Mantle cell - Diffuse large B-cell (DLBCL) - Burkitt's	T cell precursor - T-cell Leukemia/lymphoma Mature T-cell lymphomas - Peripheral T cell lymphoma - Anaplastic large cell (ALCL) - Mycosis fungoides

I- Precursors of B and T lymphocytes

Lymphoblastic lymphoma)(T or B cell type):

- Occurs in children.
- May be associated with lymphoblastic leukemia.

II- B-cell lymphoma:-

1- Follicular lymphoma:

Origin; from the follicle center cells (small centrocytes and large centroblasts).

- The neoplastic cells are arranged in follicular (nodular) pattern trying to recapitulate the normal nodal follicles (Fig.3.11).
- According to the proportion of centrocytes and centroblasts forming the neoplastic follicles they are classified into:
 - Follicular small cell type
 - Follicular mixed small and large cell type
 - Follicular large cell type
- The predominance of large centroblasts increases the grade of malignancy.

2- Diffuse small lymphocytic lymphoma:

They occur in old age, may be associated with chronic lymphocytic leukaemia.

Microscopic: There is replacement of the lymph node by diffuse proliferation of uniform small lymphocytes with variable numbers of large activated cells (Fig.3.12).

Prognosis: It has a good prognosis.

3- Diffuse lymphoplasmacytic lymphoma:

The neoplastic cells show plasmacytoid differentiation and may secrete immunoglobulins resulting in increased blood viscosity (Waldenstrom's macroglobulinaemia).

4- Mantle cell lymphoma:

This is a diffuse type of lymphoma of low grade malignancy.

Microscopic: Small to intermediate-sized irregular lymphocytes.

5- Marginal zone lymphoma:

This type may be nodal or most commonly in extranodal sites as the mucosa of GIT or respiratory tract where it is called MALT (mucosa-associated lymphoid tissue) lymphoma. It is of low grade malignancy.

6- Diffuse large B cell lymphoma:

It is the most common type of lymphoma in adults, accounting for about 40-50% of NHLs and carries worse prognosis than the follicular type.

Microscopic: Large neoplastic lymphocytes with large round or oval nuclei having prominent nucleoli.

7- Burkitt's lymphoma:

- This is a B-cell tumour of diffuse pattern.
- It is commonly seen in children and rarely occurs in adults.
- It is related to Epstein- Barr virus infection.

Sites: In Africans: The bones of the maxilla and mandible are initially involved (Fig.3.13a).

In western countries: It usually occurs in the terminal ileum, ovaries or kidneys.

The lymph nodes tend to be spared in both types.

Microscopic:

- Tumour cells are uniform and have round to oval nuclei with nucleoli and a rim of dense cytoplasm which contains clear lipid vacuoles.
- Mitotic figures are numerous. Phagocytosis of nuclear debris by macrophages is conspicuous in the rapidly dividing lymphomas.

with cell necrosis giving microscopic "starry sky" appearance (Fig.3.13).

III- T-cell lymphomas:

There are many types of T-cell lymphoma that arise in lymph node or mostly present in extranodal sites.

- 1- **Peripheral T cell lymphoma:** Most common adult T cell lymphoma, often disseminated and aggressive.
- 2- **Anaplastic large cell lymphoma** of high grade malignancy.
- 3- **Mycosis fungoides:**

This is a cutaneous T-cell lymphoma that presents initially by a non-specific erythrodermic rash then progress to tumour phase.

Microscopic: The epidermis and upper dermis are infiltrated by the neoplastic T- cells.

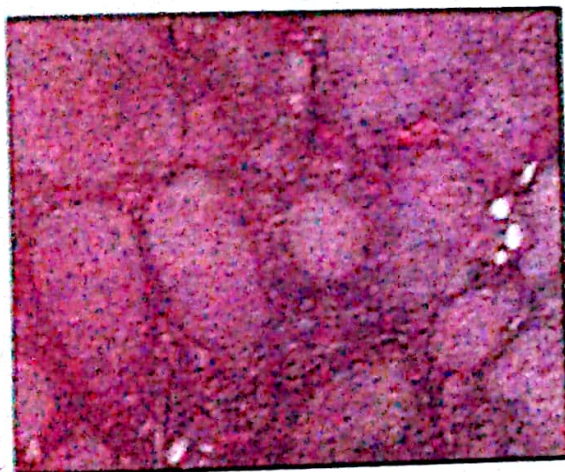


Fig.3.11: Follicular lymphoma

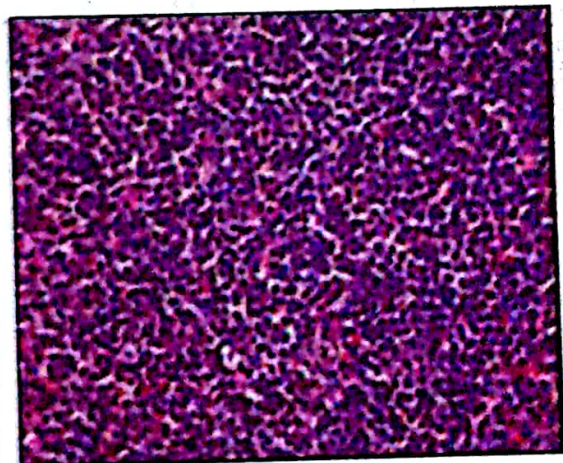


Fig.3.12: Small lymphocytic lymphoma

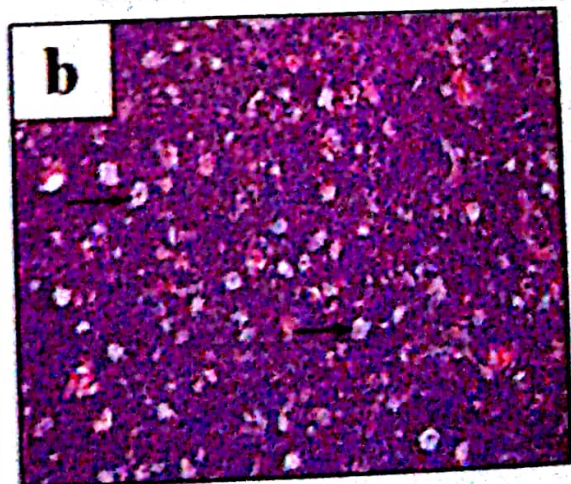


Fig.3.13: Burkitt's lymphoma (a) In the mandible (b) Starry-sky appearance

Chapter 3: Diseases of Lymph Nodes and blood

Clinical Picture of non Hodgkin lymphoma: Although each type has its own peculiar clinical picture, common clinical features are:

1. Generalized or localized lymph node enlargement.
2. Pressure symptoms manifested by the enlarged nodes on the surrounding organs.
3. Anaemia and loss of weight.

Multiple Myeloma and Related Plasma Cell Tumors:

Plasma cell neoplasms:

1- **Multiple myeloma** (discussed in chapter 12): ✓

2- **Solitary plasmacytoma**: ✓

- It involves the skeleton or the soft tissues.
- Solitary skeletal plasmacytomas usually progress to multiple myeloma over a period of 5 to 10 years.
- Soft tissues plasmacytoma is frequently spread and often cured by local resection.

3- **Monoclonal gammopathy of undetermined significance (MGUS):**

- It is the term applied to an asymptomatic monoclonal gammopathy (M proteins are found in the serum of otherwise healthy old persons).
- It is a precursor lesion with a tendency to evolve to multiple myeloma.

Causes of lymph node enlargement: →

Acute enlargement:

1. Acute lymphadenitis.
2. Infectious mononucleosis (glandular fever).
3. Typhoid fever.
4. Postvaccinal lymphadenitis following vaccination.
5. Bubonic plague.

Chronic enlargement:

1. Chronic non specific lymphadenitis.
2. Granulomatous lymphadenitis as; TB, sarcoidosis, syphilis, cat-Scratch disease and Crohn's disease.
3. AIDS related lymphadenopathy i.e. lymph node enlargement occurring with acquired immunodeficiency disease.
4. Blood diseases especially chronic leukaemias.
5. Lymphomas.
6. Metastatic tumours.

Diseases of the spleen

Congenital Anomalies:

1. Congenital absence (asplenia): It is a rare condition and usually associated with congenital heart disease.
2. Accessory spleen: It is a more common condition which may be single or multiple. It is commonly present at the tail of the pancreas or elsewhere in the abdominal cavity.

Hypersplenism:

It is a functional disorder in which the spleen is over-active with increased destruction of one or more of the three cellular components of the blood by splenic macrophages resulting in one or a mixture of anaemia, leucopenia or thrombocytopenia.

This condition may be encountered in some patients with splenic enlargement. Splenectomy is usually curative. This condition may be:

1. Primary hypersplenism: It is of unknown cause. Primary thrombocytopenia may be due to primary hypersplenism.
2. Secondary hypersplenism: It is more common and is usually secondary to other causes of splenomegaly as chronic venous congestion, bilharziasis, liver cirrhosis, lymphomas, leukaemias and myelosclerosis.

Congestive splenomegaly:

Passive chronic venous congestion and enlargement of the spleen may result from:

1. Systemic venous congestion encountered in cardiac decompensation involving the right side of the heart.
2. Intrahepatic impairment of portal venous drainage, as occurs in fibrosis or cirrhosis of the liver.
3. Obstruction of extrahepatic portal vein and splenic vein as occurs in portal or splenic vein thrombosis.

Gross: The spleen is enlarged with dark brown cut surface.

Microscopic: The red pulp is congested with red blood cells and become more fibrous with time. Organization of focal haemorrhages gives rise to foci of fibrosis containing deposits of iron and calcium salts (Gandy-Gamna nodules).

Neoplasms of the spleen:

- ☐ Benign tumours include haemangiomas, lymphangiomas and fibrosarcomas.
- ☐ Malignant tumours include primary tumours as lymphomas and haemangiosarcomas. Leukaemic deposits also may be seen in the spleen.
- ☐ Metastasis to the spleen are not common and are usually found only in very advanced malignancies.

Causes of enlargement of the spleen: (Splenomegaly)

1. Infections such as:
 - ☐ Nonspecific splenitis of various blood born infections (particularly infective endocarditis and it causes acute splenic swelling).
 - ☐ Typhoid fever (causes acute splenic swelling).
 - ☐ Infectious mononucleosis.
 - ☐ Tuberculosis and syphilis.
 - ☐ Malaria.
 - ☐ Bilharziasis.
 - ☐ Echinococcosis (hydatid cyst).
 - ☐ Toxoplasmosis.
 - ☐ Kala-azar.
2. Congestive stages:
 - ☐ Cirrhosis of the liver.
 - ☐ Portal or splenic vein thrombosis.
 - ☐ Cardiac failure (right-sided).
3. Lympho-haematogenous disorders:
 - ☐ Lymphomas.
 - ☐ Leukaemias.
 - ☐ Haemolytic anaemias.
 - ☐ Thrombocytopenic purpura.
4. Immunologic - inflammatory conditions:
 - ☐ Rheumatoid arthritis.
 - ☐ Systemic lupus erythematosus.
 - ☐ Storage diseases
 - Gaucher's disease
 - Niemann - Pick disease
 - Mucopolysaccharidosis.
5. Miscellaneous:
 - ☐ Amyloidosis.
 - ☐ Primary neoplasms and cysts.
 - ☐ Secondary neoplasms.

Diseases of thymus

The thymus is a central lymphoid organ playing an important role in T-cell differentiation. The most frequent disorders of this organ are:

1- **Thymic hyperplasia:** There is hyperplasia of the lymphoid follicles with active germinal centers. It is seen in association with a disease called myasthenia gravis (characterized by muscle weakness) and other autoimmune diseases.

2- **Thymoma:**

- They are tumours of thymic epithelial cells presenting in anterior or superior mediastinum and may be associated with myasthenia gravis.

- Thymomas are classified into:

a- **Benign (encapsulated) thymoma:** Cytologically and biologically benign

b- **Malignant thymoma:**

Type I: cytologically benign but biologically aggressive and capable of local invasion and rarely distant metastasis.

Type II: Thymic carcinoma: cytologically and biologically malignant, usually squamous cell carcinoma.

3- **Thymic T-cell lymphoma:**

Diseases of the blood

Composition of blood:

1. Plasma is an extracellular fluid containing proteins, enzymes, nutrients, wastes, hormones and gases.
2. Blood elements: RBCs, WBCs and platelets (Fig. 3.14).

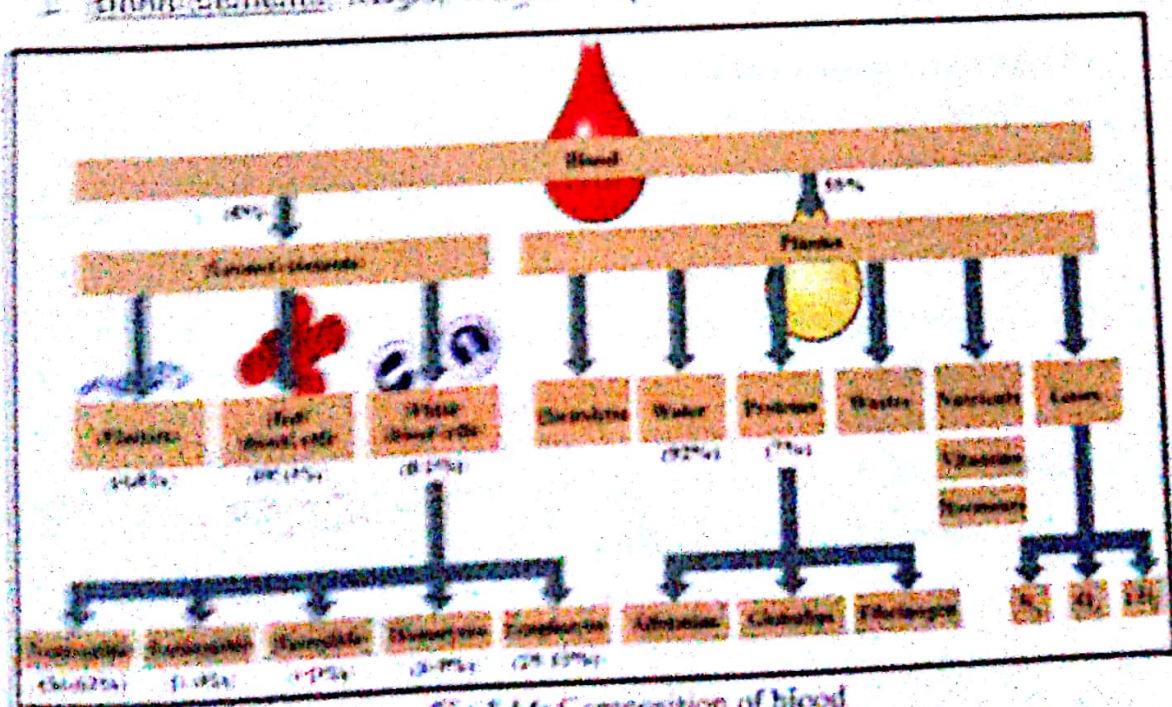


Fig. 3.14: Composition of blood

Diseases of the red blood cells:

Anaemia:

Anaemia is a condition in which there is a fall in the quantity of red cells and or haemoglobin in a unit volume of blood in the presence of a low or normal total blood volume (Fig. 3.15).

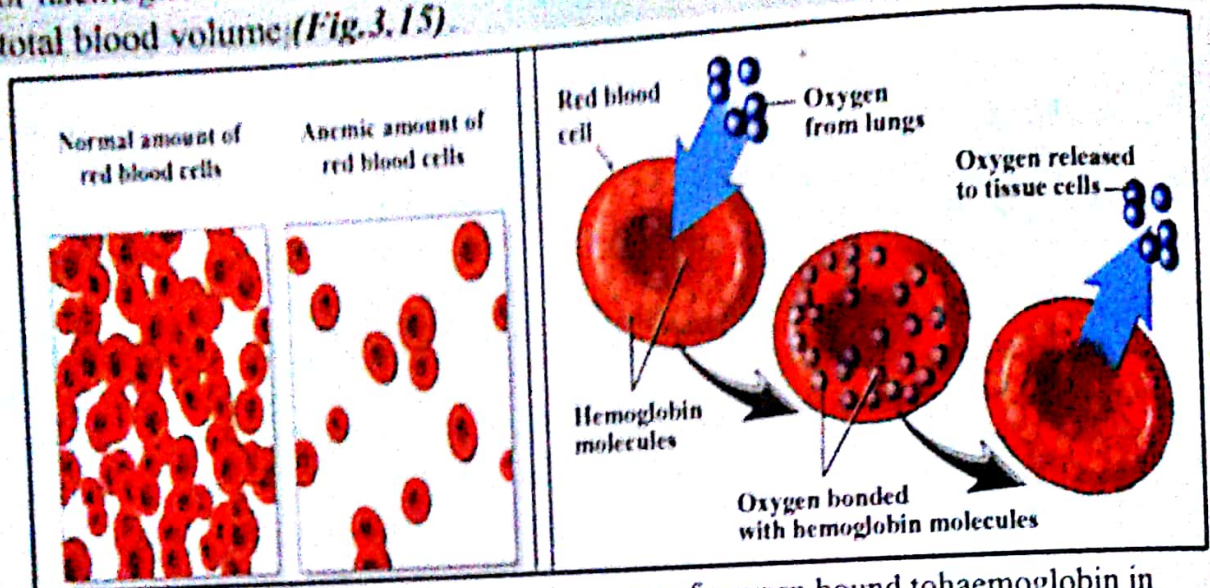


Fig 3.15: The amount of red cells and amount of oxygen bound to haemoglobin in normal and anaemic blood

Classification:

1. Deficiency anaemias:
 - a- Iron deficiency anaemia.
 - b- Megaloblastic anaemia.
2. Haemolytic anaemias: Due to excessive destruction of red blood cells and this may be:
 - a- Intracorporeal (hereditary).
 - b- Extracorporeal (acquired).
3. Bone marrow hypofunction anaemia.
4. Blood loss:
 - a- Acute: Post-haemorrhagic anaemia.
 - b- Chronic: Lesions of GI tract, gynecologic disturbances.

Pathological effects:

1. Those due to hypoxia.
2. Increased cardiac output to meet the oxygen demands of the tissues, eventually leading to heart failure.
3. Pallor of skin and mucous membranes.
4. Fatty change in parenchymatous organs.

I- Deficiency Anaemias:

A- Iron deficiency anaemia:

Causes:

1. Chronic blood loss: As in bleeding (piles, ulcers).
2. Nutritional deficiency.
3. Inadequate absorption: *inflammation of the small intestine*
4. Ankylostomiasis.

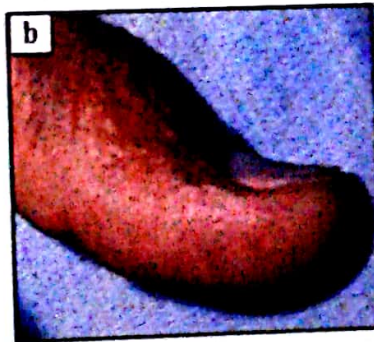
Haematological findings: Red blood cells are microcytic, hypochromic.

Pathological findings:

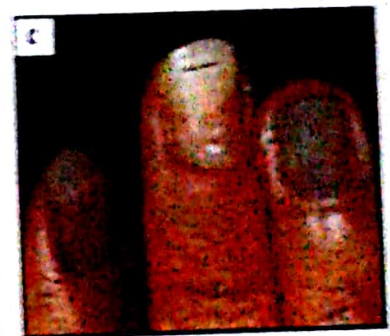
1. Oral manifestations as angular stomatitis (**Fig.3.16a**).
2. Plummer-Vinson syndrome: occurs in middle aged women with iron deficiency anaemia, glossitis, stomatitis and dysphagia. It usually leads to post-cricoid carcinoma.
3. Finger nails: Spoon shaped, brittle and lusterless (**Fig.3.16b&c**).
4. Bone marrow hyperplasia.
5. Splenomegaly. *due to reactive hyperplasia of the spleen*



Fig.3.16 (a) Angular stomatitis



(b) Spoon nails



(c) Brittle lusterless nail

B- Megaloblastic anaemia:-

Due to deficiency of vitamin B 12 or folic acid alone or in combination.

Causes:

1. Nutritional defects.
2. Pregnancy due to poor intake and increased demands of the fetus.
3. Gastric defects due to lack of the intrinsic factor.
4. Intestinal malabsorption.
5. Chronic liver disease as cirrhosis.

Pernicious anaemia or Addison's anaemia:

- ❑ It is mainly due to deficiency of vitamin B₁₂.
- ❑ With a familial tendency, common in subjects of blood group A.
- ❑ It could be either due to genetic failure of gastric mucosal cells to produce the intrinsic factor or an autoimmune disease where antibodies cause mucosal atrophy.

Haematological findings:

1. Marked diminution of red blood cell count and haemoglobin.
2. Red blood cells are macrocytic, normochromic with marked anisocytosis (variation in size) and poikilocytosis (variation in shape).

Pathological findings:

1. Haemosiderosis in parenchymatous organs due to continued absorption of iron which is not adequately used for erythropoiesis.
2. Subacute combined degeneration of the spinal cord (B₁₂ deficiency).
3. Evidence of increased haematopoiesis:

- b- Extramedullary foci of haematopoiesis in liver and spleen.
- a- Moderate splenomegaly (pernicious anaemia).

N.B.: Neurological changes do not occur in patients with folic acid deficiency.

II- Haemolytic anaemias:

A- Intracorpuseular defect (Hereditary):

1. Hereditary spherocytosis:

Carried as an autosomal dominant gene. There is a defect in RBCs membrane; abnormally permeable to sodium ions.

2. Haemoglobinopathies (Abnormal haemoglobins):

a- Sickle cell disease (Hb S)

- Sickling occurs due to the insolubility of Hb-S and occurs when oxygen tension is reduced.

a- Thalassaemia (Mediterranean or Cooley's anaemia "Hb F")

- This occurs in Mediterraneans. The production of B-chains of globin is impaired. Hb is of the fetal type (Hb-F). The red blood cells become small, hypochromic, thin (leptocytes) with central thickness (target cells).
- They are fragile and easily destroyed.

3. Enzyme-deficient RBCs:

- Due to glucose-6-phosphate dehydrogenase deficiency in RBCs.
- The RBCs are susceptible to haemolysis after administration of certain drugs as primaquine, sulphonamides, phenacetin and aspirin or ingestion of fava beans (*vicia faba*) leading to favism.

B- Extracorpuscular defects (Acquired):

1. Auto Antibodies: As Hodgkins, systemic lupus erythematosus.

2. Iso-antibodies:

Erythroblastosis fetalis: In which the red blood cells of an Rh-positive infant are destroyed by antibodies from his Rh-negative mother, after she has been previously sensitized either by a transfusion of Rh-positive blood or by an Rh-positive child born before this one.

These antibodies cross the placenta in the second pregnancy leading to haemolysis of the infant's red blood cells (Fig.3.17).

- 3. Infective agents: as toxins of Cl. Welchii and haemolytic streptococci or parasitization of RBCs in malaria.
- 4. Poisons: as snake venom or certain drugs if given in large amount as phenylhydrazine, arsenic and lead.

Pathological findings:

- 1. Bone marrow hyperplasia.
- 2. Extramedullary haematopoiesis.
- 3. Splenomegaly
- 4. Haemosiderosis.
- 5. Gall stones.

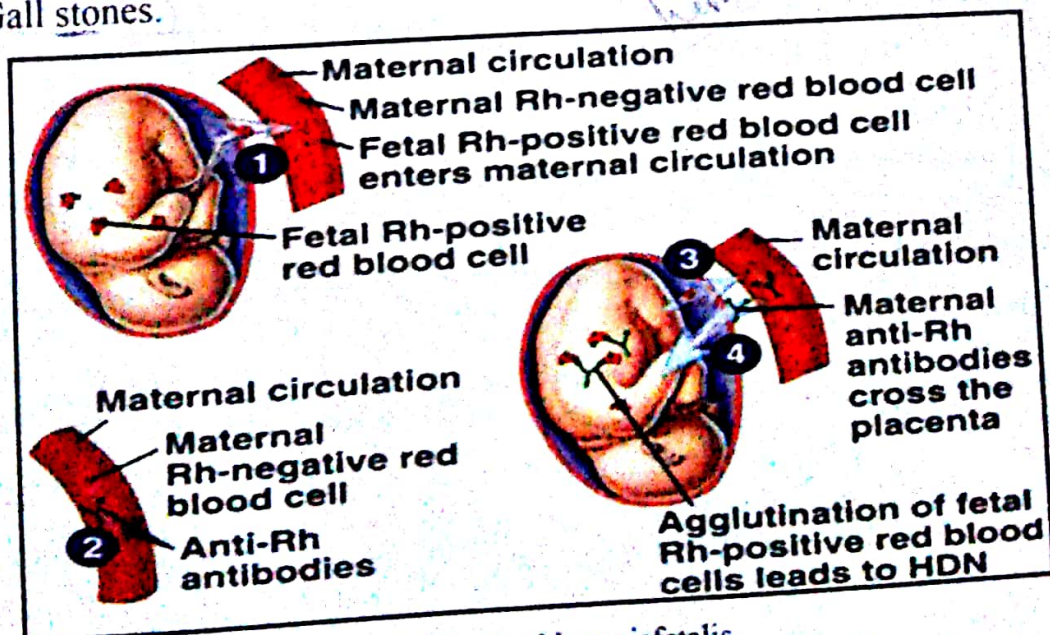


Fig.3.17: Erythroblastosis fetalis

III- Bone marrow hypofunction anaemias:

A- Aplastic anaemia: Due to bone marrow aplasia with depression in the formation of RBCs, white blood cells and platelets.

Causes:

1. Primary (idiopathic) of unknown cause.
2. Secondary to:
 - a- Idiosyncrasy (hypersensitivity) to certain drugs as amidopyrine, sulphonamides, chloramphenicol, phenyl butazone etc.
 - b- Chemical and physical poisons as benzene or ionizing radiation.

B- Leuco-erythroblastic anaemia (myelophthisic anaemia):

The bone marrow is replaced by another tissue as metastatic tumours, myelosclerosis and lipid storage disease.

Polycythemia:

Polycythemia is the increased number of RBCs in a unit volume of blood in the presence of increased blood volume.

Polycythemia is of two types:

A. Primary polycythemia (Polycythemia rubra vera):

It is considered as a neoplastic disease involving the normoblastic series of the bone marrow.

Hematological findings: -

- a- The red blood cell count is increased usually over 10 million/cmm.
- b- The Hb percentage is increased.
- c- Leucocytosis and thrombocytosis (increased number of platelets).

Pathological findings:

- 1- Cyanosis due to venous engorgement.
- 2- Enlargement of liver and spleen with foci of extramedullary haematopoiesis.
- 3- Increased tendency to thrombosis due to the high platelet count and increased viscosity of blood.
- 4- Liability to haemorrhages from mucous membranes due to fullness of small vessels with blood.
- 5- Peptic ulceration due to thrombosis of gastric small arteries.
- 6- Chronic myeloid leukaemia and myelosclerosis may develop.

B. Secondary polycythemia:

The increase in red blood cells is neither accompanied by leucocytosis nor increased number of platelets.

Causes of secondary polycythemia:

- a- Hypoxia: as in high altitudes, cyanotic congenital heart disease and chronic pulmonary disease.
- b- Renal disease: as hypernephroma, polycystic kidney and hydronephrosis due to secretion of an erythropoietin-like substance

Diseases of the white blood cells

Variations in white blood cell counts: -

Causes of neutrophilic leucocytosis (neutrophilia):

1. Infection by pyogenic bacteria, fungi, viruses or parasites.
2. Bone marrow neoplasia e.g. polycythemia vera.

Causes of lymphocytosis:-

1. Acute infection e.g. whooping cough.
2. Chronic infection e.g. tuberculosis and syphilis.
3. Infectious mononucleosis.

Eosinophilia: is observed in:

1. Infestation by parasites as bilharziasis, trichinosis and hydatid disease
2. Allergic states as asthma.

Agranulocytosis: -

It is the reduction in the number of granulocytes below 2,000/cmm.

- ☐ May be a part of total bone marrow aplasia or may occur separately.
- ☐ It is of bad prognosis and fatal.
- ☐ Characterized by marked decrease in resistance that leads to:
 1. Severe infections as bronchopneumonia.
 2. Agranulocytic angina with severe ulceration of mucous membrane.

Leukaemia:

It is a malignant proliferation of the white cell series in the bone marrow i.e. leucoblastic series. This leads to a marked increase in total white cell count with the appearance of immature cells both in the peripheral blood and tissues of the body.

Rarely, the total white blood cell count is normal or low but immature series are invading the peripheral blood, this is called **aleukaemic**

Causes:

1. Viruses.
2. Chemical agents as benzene.
3. Ionizing radiation.
4. Congenital chromosomal abnormalities.

Classification:

1. Chronic leukaemia:
 - a- Myeloid (myelocytic).
 - b- Lymphatic (lymphocytic).
2. Acute leukaemia:
 - a- Myeloid (myeloblastic).
 - b- Lymphatic (lymphoblastic).
 - c- Monocytic (monoblastic).

Chronic leukaemia:

A- Chronic myeloid leukaemia:

Haematological findings:

- 1- Total white cell count:
 - Markedly increased reaching up to 800,000 cells/cmm.
 - There are PNL with many myelocytes and metamyelocytes and few myeloblasts.
- 2- Increased eosinophils and basophils with their myelocyte precursors.
- 3- RBCs show late normochromic, normocytic anaemia due to haemolytic process or inadequacy of BM.
- 4- Blood platelets show late thrombocytopenia.
- 5- Bone marrow is hypercellular and leucoblastic.

Pathological findings:

1- Spleen:

Gross: Markedly enlarged, dark in colour and shows infarction due to leukaemic thrombi.

Microscopic: -The lymphoid follicles are atrophied.

-The red pulp is infiltrated with leukaemic cells i.e., myelocytes and myeloblasts with areas of myeloid metaplasia.

- 2- Liver is enlarged due to diffuse infiltration of portal tracts and sinusoids with leukaemic cells.
- 3- Lymph nodes show late affection.
- 4- Other organs can also be affected.

5. Anaemia with fatty change in parenchymatous organs.
6. Thrombocytopenia leading to haemorrhages.
7. PNLs are increased in number, yet are unable to perform their function as phagocytes resulting in secondary bacterial infections.

B- Chronic lymphocytic leukaemia:

It is commonly occurring in adult.

Haematological findings:

1. The total white cell count is raised between 20,000 up to 250,000 cells/cmm. About 90% of these cells are mature lymphocytes with some lymphoblasts.
2. The red blood cells show normocytic, normochromic anaemia.
3. The blood platelets: moderate thrombocytopenia.
4. The bone marrow shows late absolute increase of lymphocytic series.

Pathological findings:

1. Lymph nodes show marked generalized enlargement with diffuse infiltration by lymphocytes; a picture resembling malignant lymphoma.
2. The spleen is slightly enlarged with hyperplastic lymphoid follicles.
3. The liver is enlarged due to leukaemic infiltration mainly in portal tracts.
4. Skin and mucous membranes: Show nodules of leukaemic cells.
5. Anaemia with fatty change, haemorrhages and secondary bacterial infections; similar to those occurring in chronic myeloid leukaemia.

Fate of chronic leukaemia:

- Untreated cases are invariably fatal within 1-5 years.
- **Chronic myeloid leukaemia** is more rapidly fatal, where the cause of death is acute exacerbation.
- **Chronic lymphocytic leukemia** has a slower course with up to 10 years survival and the cause of death is inter current disease.

Acute leukaemia:

- ❑ It occurs more commonly in children and young adults but may occur rarely in adults and in old age.
- ❑ It runs a rapid and fulminating course.
- ❑ The disease is heralded by high remittent fever, rapid anaemia, bleeding manifestations, necrotic lesions of mouth and throat with some enlargement of lymph nodes, spleen and liver.

Haematological findings:

1. The white blood cell count is moderately raised up to 100,000 cells/cmm. Most of the cells are immature or blast cells with very few mature cells.
2. Marked normocytic, normochromic anemia.
3. Thrombocytopenia.

Haemorrhagic blood diseases

A- Haemorrhagic diseases due to platelet abnormalities:

Thrombocytopenic purpura:

This is due to low platelet count. It could be primary or secondary.

I- Primary (essential or idiopathic) Thrombocytopenic purpura:

It occurs in children and young adults.

It is manifested by bleeding everywhere in skin, mucous membranes, menorrhagia, melena etc... Occasionally the spleen is palpable.

Pathogenesis:

- The spleen could have a role.
- It may also have an autoimmune basis.

II. Secondary thrombocytopenic purpura: It may occur in:

1. Other blood diseases as acute and chronic leukaemia, marrow aplasia and hypersplenism.
2. Following administration of chemical (e.g. idiosyncrasy to drugs) or physical agents (e.g. ionizing radiation, burns...).

B- Haemorrhagic diseases due to vascular damage:

1. Anaphylactoid (allergic) purpura of Henoch-Schonlein:

- ☐ It is a rare allergic disease occurring in young adults.
- ☐ There is diffuse vasculitis involving the small blood vessels.
- ☐ It is characterized by skin lesions as urticaria and purpuric spots, arthritis, pain, abdominal colic due to extravasation of blood in the bowel wall, haematuria due to haemorrhages in the kidney precipitating acute glomerulonephritis.

2. Scurvy:

- ☐ Due to deficiency of vitamin C. It is manifested by bleeding from the gums and skin.
- ☐ It is due to inadequate collagen/fibers within the interstitial tissue leading to poor support of blood vessels.

Chapter 3: Diseases of Lymph Nodes and blood

Infections:

Due to toxic capillary damage as in septicemia, diphtheria and typhoid.

C - Haemorrhagic diseases due to defects in clotting mechanism:

1. Haemophilia:

It is a rare disease, inherited as X-linked recessive trait.

Affected males exhibit the disease, while females transmit it to the next generation.

Causes: There is low production of factor VIII or antihaemophilic factor (haemophilia A).

Pathological findings:

- a- Bleeding either from natural orifices or after injury or incisions.
- b- Recurrent haemarthrosis i.e. bleeding in joints, preceded by minor injury leading to crippling deformity due to fibrous adhesions.

2. Christmas disease:

It is inherited as an X-linked recessive trait, due to deficiency of factor IX (haemophilia B).

3. Hypoprothrombinemia:

- a- Congenital hypoprothrombinaemia (autosomal recessive).
- b- Acquired hypoprothrombinaemia: Due to vitamin K deficiency. This is a fat soluble vitamin, imperfectly absorbed in malabsorption syndrome, obstructive jaundice and cannot be used by the liver in prothrombin synthesis in hepatic failure.

SUMMARYDiseases of lymph nodes:Inflammatory and hyperplastic diseases

Chronic non-specific lymphadenitis: Follicular, paracortical hyperplasia & sinus histiocytosis.

Granulomatous lymphadenitis: TB, sarcoidosis, cat scratch disease, toxoplasmosis.

Primary tumours of lymphoid tissue (Lymphoma):

A- Hodgkin's lymphoma: Nodular sclerosis, mixed cellularity, lymphocyte predominance and lymphocyte depletion type.

B- Non- Hodgkin B-cell lymphoma: Lymphoblastic, follicular, diffuse small lymphocytic, diffuse lymphoplasmacytic, mantle cell, marginal zone, diffuse large B cell & Burkitt's lymphomas

T-cell lymphomas: Peripheral T cell, anaplastic large cell lymphoma, and mycosis fungoides.

Diseases of spleen:

Hypersplenism: Primary and secondary hypersplenism.

Congestive splenomegaly.

Neoplasms of the spleen: Benign as haemangiomas, lymphangioma, malignant lymphomas and haemangiosarcomas. Metastasis are rare.

Diseases of thymus

Thymic hyperplasia. Thymoma and T-cell lymphoma.

Diseases of the blood:Deficiency anaemia:

A- Iron deficiency anaemia, megaloblastic anaemia.

B- Haemolytic anaemias: spherocytosis, haemoglobinopathies and erythroblastosis fetalis.

Bone marrow hypofunction anaemias: Aplastic anaemia.

Anemia due to blood loss: post-haemorrhagic, anaemia of chronic diseases.

Leukemias: A malignant proliferation of the white cells in bone marrow with marked increase in the total white blood cell count.

Chronic leukaemia: Myeloid and Lymphatic.

Acute leukaemia: Myeloid, lymphoblastic and monocytic.

Haemorrhagic blood diseases: Purpura, haemophilia.

Chapter 4

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- ☐ Identify types of stomatitis.
- ☐ Define leucoplakia and list its causes.
- ☐ Enumerate ulcers and tumours of the oral cavity.
- ☐ Define sialadenitis and identify its types.
- ☐ Classify tumours of the salivary glands and describe the pathologic features of each.
- ☐ Define reflux oesophagitis and Barrett's oesophagus.
- ☐ Classify tumours of the oesophagus.
- ☐ Identify causes of chronic gastritis and understand the role of *H. pylori* infection in its pathogenesis.
- ☐ Describe causes, pathogenesis and sites, gross and microscopic features of peptic ulcer and list complications.
- ☐ Identify types of gastric polypi.
- ☐ Describe the pathological features of gastric adenomas.
- ☐ Classify malignant tumours of the stomach, list predisposing factors and aetiology of gastric adenocarcinoma.
- ☐ Compare intestinal and diffuse types of gastric adenocarcinomas.
- ☐ Describe the pathology of gastric lymphoma & carcinoid tumor.
- ☐ Describe the pathologic features gastrointestinal stromal tumor.
- ☐ Define haematemesis and enumerate its causes.
- ☐ Understand Meckel's diverticulum, its gross and microscopic features and complications.
- ☐ Identify typhoid fever and T.B. enteritis, describe their pathologic features and list their complications.
- ☐ Define malabsorption syndrome and understand the defects in different malabsorptive diseases.
- ☐ Compare between Crohn's disease & ulcerative colitis.
- ☐ Enumerate tumours of the small intestine.
- ☐ Describe pathogenesis, gross and microscopic features of Hirschsprung's disease.
- ☐ Describe pathology of bacillary dysentery and amoebic dysentery.
- ☐ Identify colorectal carcinoma, describe pathogenesis (including genetic factors) and pathologic features and prognostic factors.
- ☐ Describe the pathology of acute appendicitis.

DISEASES OF THE GASTROINTESTINAL TRACT

Diseases of the oral cavity

Stomatitis:

It is inflammation of mucous membrane of the mouth.

Types:

1. Aphthous stomatitis:

- ☐ It is more common in early ~~adult life~~, affecting 40% of the population.
- ☐ It may be associated with ~~inflammatory bowel disease, celiac disease and Behcet disease~~.
- ☐ ~~Single or multiple, round or oval, small, grayish, painful shallow ulcers develop on the lips, buccal mucosa and tongue.~~
- ☐ ~~The ulcers resolve in 10-14 days to recur at a later date.~~

2. Herpetic stomatitis:

- ☐ ~~Herpes simplex virus, type I and II infect oral mucosa, but type I is more common.~~
- ☐ ~~The lesions are very commonly associated with upper respiratory tract infections, immunosuppression and exposure to extremes of temperature.~~
- ☐ ~~Groups of small vesicles develop on the gingiva, lips, palate and tongue.~~

3. Agranulocytic angina:

It is a ~~severe inflammation of the gums, mucous membrane of mouth and nasopharynx with necrosis and ulceration of the mucosa.~~
It occurs in cases of ~~agranulocytosis.~~

4. Candidiasis (oral thrush):

- ~~Candida albicans is a normal commensal of the mouth.~~
- ~~Common in immunosuppressed persons e.g. new born infants, diabetic patients or those receiving chemotherapy or long term antibiotics.~~
- ~~Candida produces a superficial curdlike inflammatory membrane composed of matted organisms in a fibrinous exudate, that can be readily scrapped off leaving erythematous base.~~

5. Syphilis of the mouth: See part I General Pathology.

Chapter 4: Diseases of the gastrointestinal tract

Leukoplakia and erythroplakia: -

Leukoplakia: is a white patch or plaque that cannot be scraped off and cannot be characterized histologically as any other disease.

Erythroplakia: is a red patch without an associated inflammation.

They are common in males, between 40 and 70 years.

Aetiology: it is multifactorial, but tobacco use is the most common factor.

Site: Usually encountered in the gums, floor of the mouth and lateral borders of the tongue.

Effects: Both conditions are precancerous, but erythroplakia is associated with a much greater risk of malignant transformation.

Tumours of the oral cavity

A. Benign tumours:

1. **Squamous cell papilloma.**
2. **Cavernous haemangioma:** It affects the lip or tongue leading to macrocheilia and macroglossia respectively.
4. **Cavernous lymphangioma,** fibroma and lipoma are rare.
5. **Tumours of minor salivary glands,**

B. Malignant tumours:

Carcinoma of the mouth:

It usually occurs over 50 years of age, more common in men than in women.

Pathogenesis

- Precancerous lesions as: leukoplakia and erythroplakia.
- The major aetiological factors associated with oral cancer are tobacco use, alcohol consumption and less commonly viruses (HPV).

Site:

- The most common locations are: the ventral surface of the tongue, floor of mouth, lower lip, soft palate and gingiva.

Gross:

- Early it appears as a raised firm pearly plaque, or an irregular roughened or a verrucous mucosal thickening.
- These lesions enlarge to form ulcerated and protruding masses that have irregular borders.
- Patches of leukoplakia or erythroplakia may be found.

Microscopic:

Squamous cell carcinoma with variable degrees of differentiation.

Chapter 4: Diseases of the gastrointestinal tract

Spread:

- Local spread.
- Lymphatic spread, to submental, submaxillary, deep cervical and even to supraclavicular lymph nodes.
- Blood spread, to lung and liver may occur as a late manifestation.

Effects and complications:

- Fixation of the tongue. *infiltration downward*
- Secondary pyogenic infection leading to aspiration pneumonia and lung abscess.
- Haemorrhage.
- Cancer cachexia.

Ulcers of the tongue:

- Simple traumatic ulcer, with ragged tooth or ill fitting dentures.
- Aphthous ulcer and herpetic ulcers.
- Tuberculous ulcer, a rare complication to open pulmonary tuberculosis. The ulcer typically has undermined edges. *superficial peripheral abscess*
- Syphilitic ulcer: chancre, mucous patches or ulcerated gumma. *undermined edges, caseating ulcer*
- Malignant ulcer: has raised everted edges, necrotic infected floor and indurated base.

Diseases of the salivary glands

Sialadenitis:

It is inflammation of the salivary glands.

Causes:

- Ductal obstruction,
- Infection, viral (mumps) or bacterial sialadenitis.
- Autoimmune disease (Sjogren syndrome). *Female*

(1) Mumps (epidemic parotitis):

- o It is a common infectious disease involving the parotid glands.
- o It is most often seen in children and is caused by a paramyxovirus.

Clinical: Unilateral or bilateral enlargement of the parotid glands, accompanied by local pain, fever, malaise and headache.

Microscopic: There is interstitial mononuclear inflammatory infiltrate (Lymphocytes and histiocytes).

Course and complications:

- In children it is a self-limited condition.

Chapter 4: Diseases of the gastrointestinal tract

- In adults the following complications may occur:

1. **Orethritis**, that sometimes causes sterility.
2. **Inflammation of the ovary** may occur in adult females.
3. **Pancreatitis**, rare.

(2) **Bacterial sialadenitis**:

Most often involves the **minor salivary glands** particularly the **submandibular**.

Causative organisms: **Staphylococci** and **streptococci**.

Predisposing factors: **Obstruction of the duct** by **stones**, **impacted food debris** or **edema** consequent to injury.

Morphology: **Unilateral involvement is the rule**.

The affected gland is **enlarged** and **hyperaemic** with **formation of pus**.

(3) **Sjogren's syndrome**:

It is an **autoimmune disease** in which there is **immune-mediated destruction of the lacrimal and salivary glands**.

Clinically it is manifested by:

- **Dry eyes** (**kerato-conjunctivitis sicca**).
- **Dry mouth** (**xerostomia**) due to **failure of gland secretion**.

Sialolithiasis (Salivary calculi):

- **Salivary stones** are common; mostly occurring in the **submandibular duct**.
- **Rarely other salivary glands** are affected as they **secrete watery secretion**.
- The **stone is formed of a nidus of desquamated ductal epithelium** and **inspissated secretion** with **overlying laminated calcium phosphate concretions**.
- The patient complains of **pain and enlargement of the gland at meal time** due to **accumulation of secretion** which **gradually subsides after meal**.
- It **predisposes to suppurative inflammation of the gland**.

Tumours of the salivary glands

A. Benign tumours:

1. Pleomorphic adenoma (mixed salivary tumour):

- It accounts for more than 50% of salivary gland tumours.
- The **parotid gland** is more commonly affected than the other major or minor glands.
- It is **more common in females** than males in the 4th decade of life.

Gross (Fig.4.1a):

- The tumour is **encapsulated**, but in **some cases the capsule is not fully**

Chapter 4: Diseases of the gastrointestinal tract

- ~~developed with tumour protrusions into the surrounding structures.~~
- ~~The cut surface is firm, greyish-white and contains myxoid areas.~~

Microscopic: It is a heterogeneous tumour composed of:

- ~~Epithelial elements: epithelial duct-like structures intermixed with solid sheets or strands of spindle shaped myoepithelial cells.~~
- ~~Mesenchymal elements: loose myxoid tissue containing islands of chondroid and areas of bone (Fig. 4.1b).~~

NB: Recurrence occurs after removal of the tumour in about 25% of cases due to failure to recognise minute extensions of tumor beyond the capsule.

2. Papillary cystadenoma lymphomatosum (Warthin's tumour):

It is limited to the parotid gland and more common in elderly males.

Gross: It is encapsulated, the cut surface exhibits large cystic areas (Fig. 4.2a).

Microscopic: It shows large cystic spaces crowded with papillary projections, which are covered by a regular array of columnar oncocytes, beneath which are sheets of mature lymphocytes sometimes forming follicles with germinal centres (Fig. 4.2b).

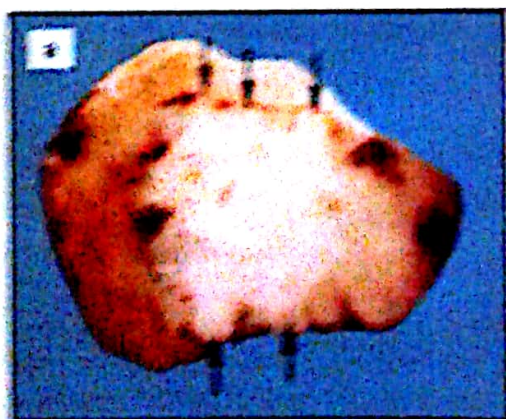
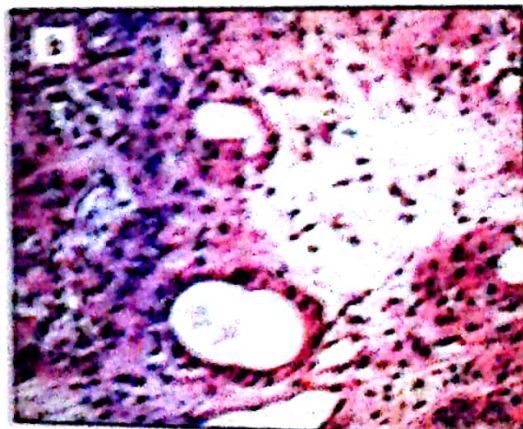


Fig. 4.1: Pleomorphic adenoma. a) Gross.



b) Microscopic.

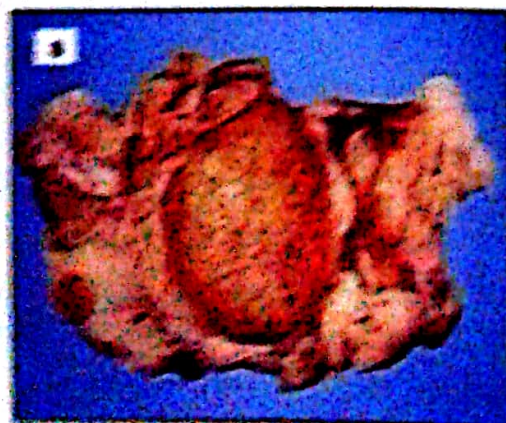


Fig. 4.2: Warthin's tumour. a) Gross.



b) Microscopic.

B. Malignant tumours:

1. Mucoepidermoid carcinoma:

- It is the commonest primary malignant tumour of salivary glands.
- It represents about 15% of all salivary gland tumours. The majority arise from the parotid (60-70%) followed by minor salivary glands.

Gross: It is apparently circumscribed, but not encapsulated and is often infiltrative. The cut surface is pale gray to white with small mucinous cysts.

Microscopic (Fig.4.3):

- It consists of mucous, epidermoid and intermediate cell types.
- The neoplastic cells are arranged in cords, sheets or cysts.
- Cytologically, the tumour cells may be benign appearing or highly anaplastic. On this basis, mucoepidermoid carcinoma is subclassified into low, intermediate and high grade.

Spread: locally and to regional lymph nodes especially with the high grade tumours.

2. Adenoid cystic carcinoma:

- It accounts for about 10% of all salivary tumours.
- It is the most common malignant tumour of submandibular and minor salivary glands.
- It is slowly growing, however, it is an infiltrative aggressive tumor which can metastasize even many years after excision.

Gross: The tumour is white and glistening with infiltrative margins.

Microscopic:

- The classic cylindrical type is composed of small monomorphic myoepithelial cells with hyperchromatic nuclei surrounding pseudoglandular spaces (Fig.4.4).
- Perineural invasion is common.

3. Carcinoma in pleomorphic adenoma:

- The incidence of malignant change increases with time reaching 10% after 15 years.
- The cancer usually takes the form of adenocarcinoma or undifferentiated carcinoma.

4. Undifferentiated carcinoma: A rare tumour.

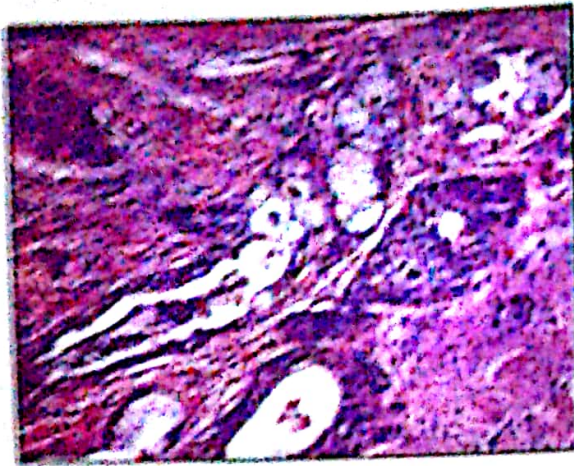


Fig.4.3: Mucoidermoid carcinoma.

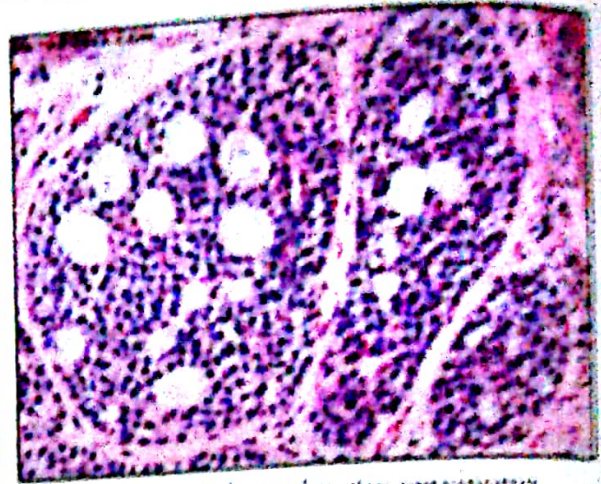


Fig.4.4: Adenoidcystic carcinoma.

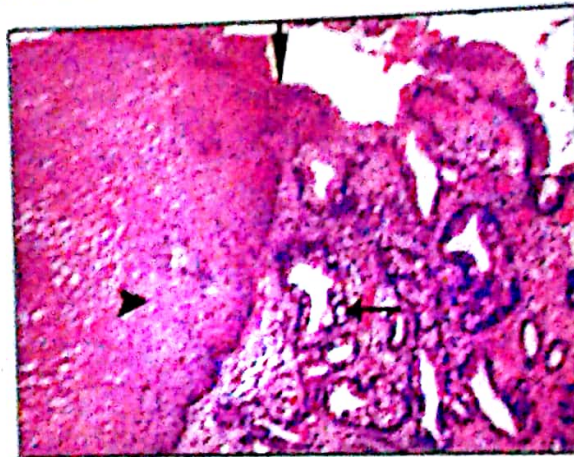


Fig.4.5: Barrett's oesophagus with intestinal metaplasia.

Diseases of the pharynx

Pharyngitis: Is similar to stomatitis with all its types.

Tumours of pharynx

A) Benign tumours:

1. Squamous cell papilloma

2. Nasopharyngeal angiofibroma

Usually arises in young adults between 15 and 25 years.

Almost exclusively in males.

It is a well circumscribed, large, highly vascular tumour mass.

3. Pleomorphic adenoma of minor salivary glands (rare).

B) Malignant tumours:

1. Squamous cell carcinoma, occurs mainly in adults with a male predilection.

2. Undifferentiated carcinoma (lymphoepithelioma);

It is a rare neoplasm that is linked to EBV infection.

Chapter 4: Diseases of the gastrointestinal tract

- It affects adults, but can occur in children.
- More common in males.
- It usually gives metastasis in the cervical lymph nodes on both sides and in the viscera as lungs, liver and bones, before attaining a large size or even before it is seen clinically.

Microscopic: Undifferentiated carcinoma with prominent lymphoplasmacytic infiltrate.

Diseases of the oesophagus

Oesophageal varices:

- These are tortuous, dilated veins lying primarily within the submucosa of distal oesophagus and proximal stomach with irregular protrusion of overlying mucosa into the lumen.
- Rupture may occur, with severe and fatal haematemesis.
- It is caused by portal hypertension due to any cause e.g. cirrhosis and bilharzial portal fibrosis of liver.

Oesophagitis (inflammation of the oesophagus):

Causes:

1. Acid reflux through the gastro-oesophageal junction (reflux oesophagitis)
2. Ingestion of irritants as corrosives leading to chemical oesophagitis.
3. Infections: Mainly occur in immunocompromised hosts as fungal (candida albicans) and viral as herpes simplex (HSV) and cytomegalovirus (CMV). Bacterial infection is rare.
4. Physical as radiation.

Reflux oesophagitis:

- Reflux of gastric contents into the distal oesophagus is the most frequent cause of esophagitis.
- The associated clinical condition is termed gastro-oesophageal reflux diseases (GERD).

Gross:

- The mucosa of the lower oesophagus appears red with superficial erosions.
- In advanced cases, ulceration and fibrous narrowing can occur.

Microscopic:

- Hyperplasia of the basal cells of the squamous epithelium that extends to more than 20% of mucosal thickness.

- Marked elongation of the lamina propria papillae.
- Infiltration of the epithelium by neutrophils and eosinophils.
- Superficial necrosis and ulceration in severe cases.

Complications:

1. Peptic ulceration.
2. Scarring, leading to stricture formation.
3. Barrett's oesophagus.

Barrett's oesophagus:

It is a metaplastic change of the lower oesophageal epithelium from squamous to columnar (usually intestinal-type epithelium).

- It occurs in 10% of patients with symptomatic reflux oesophagitis.
- It is diagnosed by endoscopy with biopsy > 3cm above the gastro-oesophageal junction (Fig.4.5).
- Patients have an increased risk of developing adenocarcinoma.

Tumours of the oesophagus

A- Benign tumours:

Squamous cell papilloma, neurofibroma, haemangioma, etc....

B- Malignant tumours:

(1) Carcinoma of the oesophagus:

It is a common tumour, occurring more in males over age of 45 years. Oesophageal cancer may be adenocarcinoma or squamous cell carcinoma. Worldwide, squamous cell carcinoma is more common but the incidence of adenocarcinoma increases and now accounts for half of all oesophageal cancers in US.

Predisposing factors:

- Alcohol, tobacco use.
- Previous radiation therapy to the mediastinum.
- Achalasia, caustic oesophageal injury, oesophageal diverticula, Plummer-Vinson syndrome (Dysphagia, iron deficiency anaemia, and oesophageal webs) and consumption of very hot beverages (squamous cell carcinoma).
- Reflux oesophagitis with Barrett's oesophagus (adenocarcinoma).

Sites: Nearly half of invasive squamous cell carcinomas are located in middle third of the oesophagus. Adenocarcinomas are located in distal third of the oesophagus.

Chapter 4: Diseases of the gastrointestinal tract

Gross:

- ~~Fungating, polypoid mass protruding into and obstructing the lumen.~~
- ~~Ulcerating or diffusely infiltrative tumour that causes thickening, rigidity and narrowing of the lumen.~~

Microscopic:

- ~~Squamous cell carcinoma.~~
- ~~Adenocarcinoma typically arises in cases of Barrett's oesophagus.~~

Spread:

1. ~~Direct:~~ First in the wall of oesophagus then to the surrounding structures such as trachea, bronchi, lungs, mediastinum and rarely the aorta leading to fatal haemorrhage.
2. ~~Lymphatic spread:~~ To cervical, mediastinal or abdominal groups depending on the site of the tumour.
3. ~~Blood spread:~~ To liver, lungs etc...

(2) Other rare malignant tumours:

~~Leiomyosarcoma, rhabdomyosarcoma and lymphoma.~~

Dysphagia:

~~It means difficulty of swallowing.~~

Causes:

1. ~~Causes in the lumen e.g. impaction of a foreign body.~~
2. ~~Causes in the wall as:~~
 - ~~Congenital causes e.g. stenosis, atresia and webs.~~
 - ~~Strictures; post-inflammatory or post-traumatic.~~
 - ~~Tumours of oesophagus e.g. carcinoma.~~
 - ~~Plummer-Vinson syndrome.~~
 - ~~Achalasia:~~ A disease affecting young adults. There is failure of relaxation of cardiac sphincter with consequent oesophageal dilatation, dysphagia and regurgitation. It is caused by loss of ganglion cells in the myenteric plexus of the oesophagus. This leads to failure of propulsive peristaltic waves without which the cardiac sphincter does not relax.
3. ~~Causes outside the oesophagus: Enlarged mediastinal lymph nodes, bronchogenic carcinoma and aortic aneurysm pressing on the oesophagus.~~

Diseases of the stomach

Congenital anomalies:

1. Diaphragmatic hernias: There is weakness or defect in the diaphragm. There is herniation of a part or all of the stomach through the diaphragm.
2. Congenital pyloric stenosis: It is due to hypertrophy of the circular muscle of the muscularis propria of the pylorus.
 - It affects males more than females (4:1).
 - It manifests in the third week of life by regurgitation and vomiting.

Gastritis (inflammation of the gastric mucosa):

I. Acute gastritis:

It is a transient mucosal inflammatory process.

Causes:

- ❑ Prolonged and excessive use of drugs such as: aspirin, nonsteroidal anti-inflammatory drugs.
- ❑ Excessive alcohol consumption.
- ❑ Heavy smoking.
- ❑ Ingestion of acids and alkalis.
- ❑ Irradiation and chemotherapy.
- ❑ Old age.

Microscopic:

Mild acute gastritis: The surface epithelium is intact with neutrophilic infiltrate. Lamina propria is mildly congested, edematous with few lymphocytes and plasma cells.

Acute erosive hemorrhagic gastritis: Severe mucosal damage with focal necrosis and erosion (loss of surface epithelium), associated with neutrophilic infiltrate and hemorrhages.

Acute peptic ulcer:

Focal acute peptic injury is a common complication of NSAID and severe stress (e.g. stress ulcer in shock, severe burn, trauma or increased intracranial pressure).

II. Chronic gastritis: Types:

1- Helicobacter pylori gastritis:

- H. pylori organisms are present in 90% of cases of chronic gastritis affecting the antrum.
- This organism is a curved or comma shaped gram negative bacillus which

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produces large amounts of ~~digestive enzymes~~ and ~~toxins~~ which are injurious to the gastric mucosa.

Microscopic:

- H. pylori organisms are usually concentrated within superficial mucus overlying epithelial cells.
- Neutrophils infiltrate the lamina propria, glands and the surface epithelium. Some accumulate in the lumen of gastric pits forming small pit micro-abscesses.
- The lamina propria is infiltrated by plasma cells and lymphocytes, occasionally forming follicles.
- Intestinal metaplasia may be present.

NB: 1- Activity in chronic gastritis: means the presence of neutrophils in a background of chronic inflammation.

2- Atrophy in chronic gastritis: means the extension of the chronic inflammatory cells deeply down to the muscularis mucosa to involve and replace the gastric glands.

Clinical features:

- Patients may be asymptomatic or present with dyspeptic symptoms.

Complications:

- Peptic ulcer.
- Gastric carcinoma.
- Mucosa-associated lymphoid tissue (MALT) lymphoma.

2- Autoimmune gastritis (chronic atrophic gastritis):

- It occurs mainly in the fundus and body of the stomach.
- It accounts for 10% of cases of chronic gastritis.
- It is the most common cause of atrophic gastritis.
- It is often autosomal dominant and it is associated with:
 - Antibodies to the parietal cells and intrinsic factor in serum and gastric secretions.
 - Defective gastric acid secretion (achlorhydria).
 - Can lead to destruction of the oxyntic mucosa and pernicious anaemia.
 - In fully established cases, the body mucosa shows extensive atrophy and intestinal metaplasia.

3- Reactive gastritis.

It is due to chemicals, drugs, radiation injury or chronic bile reflux.

Peptic ulcer disease:

It is defined as a mucosal defect in any portion of the gastrointestinal tract exposed to acid-pepsin secretion.

Sites (in descending order of frequency):

1. First part of duodenum.
2. Stomach, usually the antrum.
3. The lower part of the oesophagus as a result of reflux oesophagitis.
4. In the margins of a gastroenterostomy (stomal ulcer).
5. In the duodenum, stomach or jejunum in patients with Zollinger Ellison syndrome.
6. Within a Meckel's diverticulum that contains ectopic gastric mucosa.

Age and sex incidence:

Peptic ulcer is common in adults; it affects males much more than females.

Pathogenesis:

Peptic ulcers are produced by an imbalance between the gastroduodenal mucosal defense mechanisms and damaging forces (Fig.4.6).

1. Mucosal defence mechanisms:

Several mechanisms operate to maintain the integrity of the gastroduodenal mucosa:

- Mucus forms an insoluble gel layer adherent to the mucosal surface.
- Bicarbonate secretion into mucus neutralizes the acid.
- Epithelial regeneration capacity provides cellular barrier.
- Mucosal blood flow is important to keep integrity of mucosa.
- Prostaglandins seem to have a role in cytoprotection.

Mucosal defense is impaired by: Ischaemia and shock or duodenal gastric reflux, breakdown of the gel layer induced by some drugs and impaired synthesis and secretion of mucin by surface epithelial cells (in old age).

2. Damaging forces:

Gastric hyperacidity which is due to:

- *H. pylori* infection.
- Anti-inflammatory drugs and aspirin, cigarettes, alcohol.
- Impaired regulation of acid secretion (for unclear causes).

Helicobacter pylori (*H. pylori*) plays a major role:

- The organism is present in the gastric mucosa of 90% to 100% of patients with duodenal ulcer and 70% of those with gastric ulcer.

Chapter 4: Diseases of the gastrointestinal tract

- Bacterial urease and toxins (which is encoded by Cag A gene) may be involved in ulcer or cancer development.
- Protease induced mucosal damage, predisposing to inflammation which continues the mucosal injury.

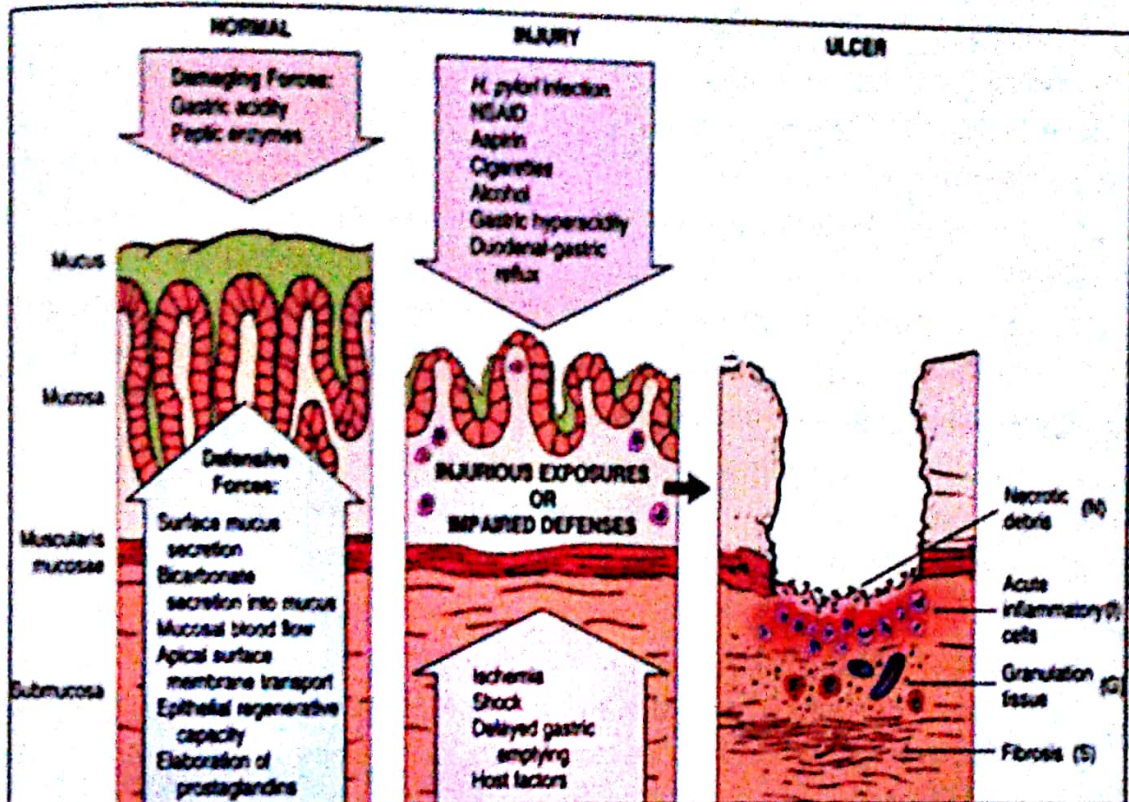


Fig.4.6: Mechanism of gastric injury and protection

Sites of peptic ulcer:

a- Gastric ulcer:-

- Lesser curvature of the stomach (About 80% of gastric ulcers).
- Rarely on greater curvature, anterior wall, posterior wall and fundus.

b- Duodenal ulcers:-

- First part of the duodenum, on the anterior or posterior wall.

Gross:

- Peptic ulcer is round and sharply punched out defect.
- It is usually solitary but two ulcers can exist (particularly in duodenum). Kissing ulcers usually in the duodenal bulb or the prepyloric antrum represent simultaneous ulcerations of the anterior and posterior walls.
- The ulcer floor appears remarkably clean and the edges are clear cut.
- The size is usually less than 2 cm, though occasional giant ulcers (8 cm or more) occur.
- The overlying serosa is often thickened and opaque.
- In gastric ulcer, the surrounding mucosa appears flattened and atrophic.

Microscopic:

During the active phase, four zones can be distinguished (Fig4.6):

- 1- A necrotic zone; lies on the floor of the ulcer and is composed of fibrinous exudates and necrotic debris.
- 2- Active non-specific inflammatory cell infiltrate rich in neutrophils.
- 3- Active granulation tissue.
- 4- Fibrosis; deep to the granulation tissue there is a dense fibro-collagenous scar, where the arterioles show thrombosis and endarteritis obliterans and the small veins may contain organized thrombi.

Clinical:

- Epigastric burn or aching pain 1 to 3 hours after meals during the day, worse at night, and is relieved by alkali or food.
- Nausea, vomiting and bloating.
- Healing may occur with or without therapy.

Complications:

1. Haemorrhage: leading to haematemesis.
2. Perforation: It leads to either a subdiaphragmatic abscess or to generalized peritonitis.
3. Cicatricial contraction leads to pyloric stenosis.
4. Penetration: It occurs if the stomach becomes adherent to the underlying organs e.g. the pancreas, then the ulcer opens through it.
5. Malignant transformation:
 - It may rarely occur in the stomach (less than 1%).
 - It is unknown with duodenal ulcer.

Gastric Polyps

Polyps are nodules that project above the level of the surrounding mucosa.

1. Inflammatory and hyperplastic polyps

- Represent approximately 75% of all gastric polyps.
- Arise on a background of chronic gastritis.
- Inflammatory and hyperplastic polyps are essentially the same entity, with the distinction based solely on the degree of inflammation.
- Development of dysplasia in inflammatory or hyperplastic polyps correlates with size; with a significant increased risk in polyps larger than 1.5 cm.

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2. Fundic gland polyps

- Fundic gland polyps occur sporadically and in persons with familial adenomatous polyposis (FAP) but do not have neoplastic potential.
- Occur in the gastric body and fundus.
- Composed of cystically dilated, irregular glands lined by flattened parietal and chief cells.

Tumours of the stomach :-

A. Benign tumours:

1. Gastric adenoma:-

- A true neoplasm with proliferative dysplastic epithelium and has a malignant potential.
- Adenomas are usually single, may be sessile (without a stalk) or pedunculated (with a stalk).
- May ulcerate leading to haemorrhage.
- Adenomas arise in the background of chronic gastritis with atrophy and intestinal metaplasia (Fig. 4.7).
- Risk of malignant change increases in polyps greater than 2cm.

B. Malignant tumours:

1) Carcinoma of the stomach: ←

- Gastric adenocarcinoma represents more than 90 % of all gastric cancers.
- It occurs more in males above the age of 45 years.

Pathogenesis of gastric carcinoma:

1. H. pylori infection: Increases the risk of chronic gastritis-associated intestinal-type gastric cancer.
2. Atrophic gastritis with intestinal metaplasia.
3. Adenoma: Up to 30% of gastric adenomas harbor carcinoma at the time of diagnosis.
4. After gastrectomy for a benign disease, there is an increased incidence of gastric carcinoma in the remaining gastric stump.
5. EBV infection: 10% of gastric cancer are associated with EBV infection.
6. Mutations of CDH1 gene (which codes for E-cadherin) are associated with familial diffuse gastric cancer (HDGC).

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Sites: It is most common in the pyloric region, pyloric antrum and on the lesser curvature.

Less common locations are the cardia, the body and the fundus.

Gross:

1. Exophytic or fungating mass which projects into the lumen (Fig. 4.8).

2. Malignant ulcer usually larger than 2.5 cm and has raised everted edges, indurated base and necrotic floor (Fig. 4.9).

3. Infiltrating carcinoma:

a- Localized infiltrating carcinoma: It occurs in the pylorus and pyloric antrum leading to thickening of the wall with pyloric stenosis.

b- Diffuse infiltrating carcinoma: The entire stomach wall is thickened (up to 2 cm) but there is no intraluminal mass. The stomach is converted into a thick, rigid and short tube called linitis plastica or leather bottle stomach (Fig. 4.10).

Microscopic:

Gastric adenocarcinomas are classified into (Table 4.1):

1. Intestinal type: Composed of glands, papillae or solid sheets of cells. The neoplastic cells are columnar and mucin producing (Fig. 4.11).

2. Diffuse infiltrative carcinoma: Composed of discohesive neoplastic cells with large intracellular mucin vacuole and a peripheral nucleus i.e. signet ring cells. These cells infiltrate the wall singly or in small clusters, evoking a prominent desmoplastic stroma (Extensive fibrosis), that makes the wall thick and rigid (Fig. 4.10b). This tumour is poorly differentiated.

Table 4.1: Differences between intestinal and diffuse gastric carcinomas.

Gastric adenocarcinoma		
Type	Intestinal type	Diffuse type
Etiology	• <u>H. pylori/metaplasia</u> • <u>Chronic gastritis/ atrophy</u> • Some cases; mutation in <u>APC & β-catenin</u>.	• <u>Idiopathic/familial</u> • <u>No precursor lesions</u> • <u>Mutation of CDH1 gene</u>
Gross	<u>Fungating mass, ulcer</u>	<u>Diffuse infiltrating</u>
Microscopic	• <u>Glands /</u>	• <u>Signet ring cells</u> • <u>Poorly differentiated</u>
Prognosis	<u>Better</u>	<u>Poor</u>

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Spread:

1. **Direct spread:** Through the wall of the stomach, then to nearby organs.
2. **Lymphatic spread:** To lymph nodes along lesser curvature or along the greater curvature, those in the portahepatis and around the coeliac axis. Involvement of the left supraclavicular lymph node - "Virchow" sign is sometimes the presenting feature of gastric cancer.
3. **Blood spread:** To the liver, then to lungs, kidneys and bones.
4. **Krukenberg tumour:** Spread of signet ring carcinoma to both ovaries via lymphatics.

Effects:

1. Haemorrhage leading to haematemesis.
2. Pyloric obstruction with vomiting.
3. Cancer cachexia with weight loss and marked anaemia.

Prognosis:

The depth of invasion and the extent of nodal and distant metastasis at the time of diagnosis are the most powerful prognostic indicators.

2) **Lymphoma:** It is usually of the diffuse non-Hodgkin's type.

3) **Carcinoid tumour:**

- It can occur anywhere in the gastrointestinal tract from the oesophagus to the anal canal and also in the bronchi.
- Gastric carcinoids are associated with endocrine cell hyperplasia, atrophic gastritis and Zollinger-Ellison syndrome.
- The most important prognostic factor in GIT carcinoids is location.
 - Foregut carcinoids (stomach and duodenum) rarely metastasize.
 - Midgut tumours (jejunum and ileum) tend to be aggressive.
 - Hindgut tumours in the appendix and colorectum are typically benign.

4) **Gastrointestinal stromal tumour (GIST):**

- It is the most common mesenchymal tumour of the gastrointestinal tract and more than half of the cases occur in the stomach.
- It arises from the interstitial cell of Cajal.
- It is common in males with a peak age incidence of 60 years.

Gross: Usually a well-circumscribed submucosal mass.

Microscopic: Composed of spindle cells or plump epithelioid cells.

- a- **Benign GIST:** Cellular proliferation of bland cells.
- b- **Malignant GIST:** The neoplastic cells show criteria of malignancy with variable degrees of mitoses (Fig. 4.12).

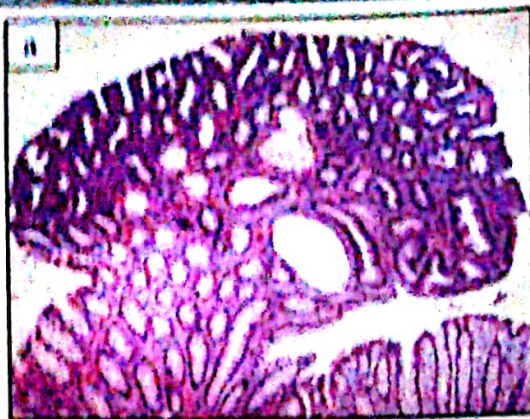
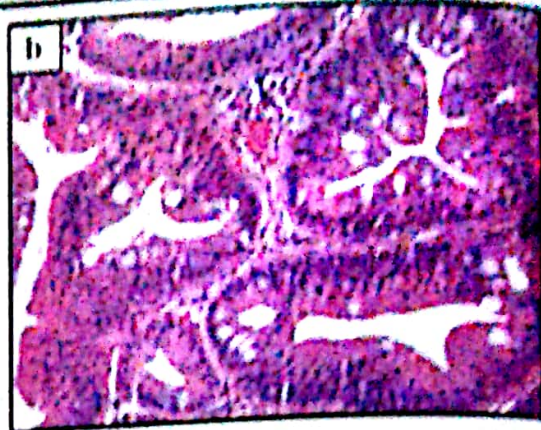


Fig. 4.7: Adenomatous polyp: a) Low power



b) High power



Fig. 4.8: Fungating gastric carcinoma

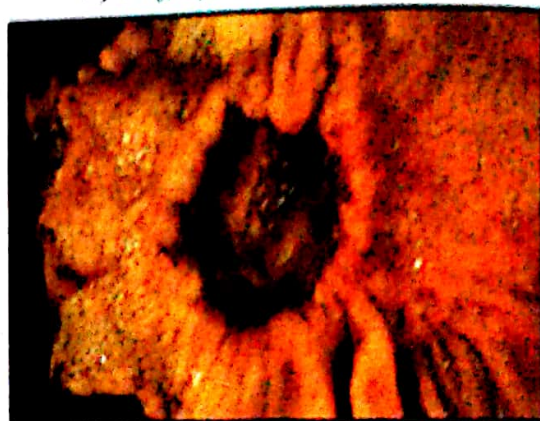


Fig. 4.9: Malignant gastric ulcer



a) Linitis plastica

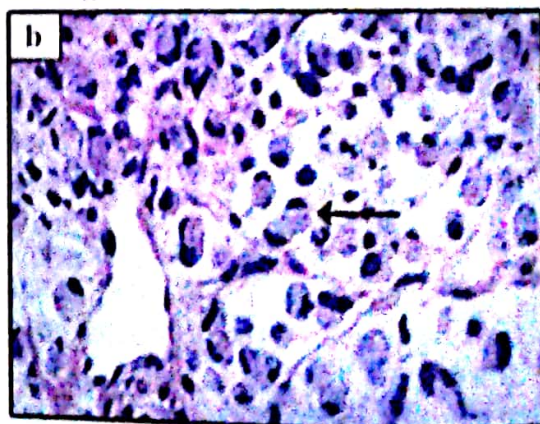


Fig. 4.10: Diffuse gastric carcinoma;

b) Signet ring carcinoma

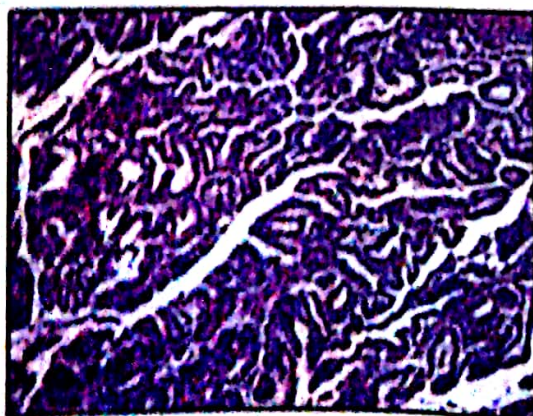


Fig. 4.11: Intestinal type gastric adenocarcinoma

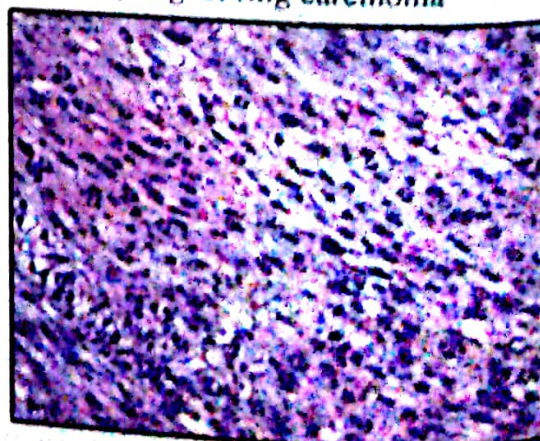


Fig. 4.12: Malignant GIST, spindle cell type

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Haematemesis:

Haematemesis is vomiting of blood.

Causes:

1. Diseases of the oesophagus:
 - a- Oesophageal varices.
 - b- Mallory-Weiss syndrome; linear oesophageal lacerations common in alcoholics.
 - c- Carcinoma of oesophagus.
 - d- Peptic ulcer of oesophagus.
 - e- Rupture of aortic aneurysm into the oesophagus.
2. Diseases of the stomach and duodenum:
 - a- Acute and chronic gastritis.
 - b- Peptic ulcer.
 - c- Gastric carcinoma.
 - d- Gastric erosion following ingestion of some drugs e.g. aspirin.
3. Generalized disease; as purpura, leukaemia, haemophilia and scurvy.

Diseases of the small intestine

1. Congenital anomalies:

1. Intestinal atresia, stenosis and malrotation.
2. Ectopic rests of normal pancreatic tissue.
3. Meckel's diverticulum.

Meckel's Diverticulum:

It is a blind-ended pouch, whose lumen communicates with the lumen of the gut. It arises from incomplete obliteration of the vitelline duct.

Gross:

- It is present in the antimesenteric border of the ileum, about 30 cm from the ileocaecal valve in children and about 90 cm in adults.
- It varies in length from 2-8 cm with a narrow patent lumen.
- The tip may be attached to the umbilicus by a fibrous band representing the remnant of the vitelline duct.

Microscopic:

The mucosa, submucosa and muscularis propria simulate that of the small intestine, heterotopic gastric, pancreatic or biliary tissue may be seen.

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Clinical:

1. The case is usually **asymptomatic**.
2. **Symptoms of peptic ulceration**.
3. **Perforation**.
4. **Intussusception**.
5. **Diverticulitis simulating symptoms of appendicitis**.

II. Inflammation:

1. Typhoid fever (Salmonella enteritis):

It is a **generalized infectious disease** affecting mainly the **lymphoid tissue** especially that of the small intestine. It is **caused by Salmonella typhi** organism.

Mode of infection:

The organism is transmitted from a **diseased person** or a **healthy carrier** by direct way or by **flies from infected and contaminated food or water**.

Gross:

- The ileum shows **multiple oval ulcers** with their longer dimensions **parallel to the long axis** of the small intestine. The floor of the ulcer is **composed of dark necrotic tissue mixed with fibrin (Fig.4.13)**.
- The **mesentric lymph nodes** are **enlarged** and the **cut surface shows areas of necrosis and haemorrhage**. *compress in I.B.V. → ulcer*
- The **spleen** is **moderately enlarged** and soft, with **tense capsule**. The **cut surface is deep red in colour**.
- The **liver** may also be **enlarged** and shows **microfoci of necrosis**.

Microscopic:

- ❑ Early there is **infiltration of the mucosa by large number of macrophages** filled with **erythrocytes and necrotic debris**.
- ❑ Later on, **necrosis of lymphoid follicles becomes confluent and ulceration of the overlying mucosa becomes evident with areas of haemorrhage**. There is **lack of neutrophils**.
- ❑ By the end of the second week **healing of the ulcer by regeneration is almost complete leaving little fibrosis**.

Complications:

1. **Toxaemia causes paralytic ileus, fatty liver, toxic myocarditis, nephritis and necrosis of the muscles of the abdominal wall, diaphragm and thigh (Zenker's necrosis)**.
2. **Perforation of the ulcer leading to suppurative peritonitis and haemorrhage**.

3. Acute and chronic cholecystitis with liability to gall stone formation.
4. Typhoid osteomyelitis especially in the tibia, sternum, ribs and spine.
5. Bone marrow infiltration by macrophages leading to leucopenia with relative monocytosis.
6. Occurrence of carrier state, after clinical recovery, the bacilli may remain in the gall bladder or in the kidneys and continue to pass intermittently in the faeces or urine.

Laboratory examination and diagnosis:

1. Blood culture is positive in the first week.
2. Stool and urine cultures are positive in the second and third weeks.
3. Widal agglutination test usually positive after the first week.
4. Peripheral blood shows leucopenia with relative monocytosis.

2) Tuberculous enteritis:

A- Primary intestinal T.B.:

Caused by **ingestion of contaminated milk**

a- Primary intestinal complex: Most common in children:

- Primary lesion: Small caseous focus in the terminal ileum
- T.B. Lymphangitis;
- Tubercles mesenterica.

b- Hypertrophic T.B.: "rare" in adults.

- Site: Ileocaecal.
- Proliferative reaction with minimal caseation.
- Fibrosis, mucosal ulceration and subserosal tubercles.
- Lymph node enlargement.

B- Secondary intestinal T.B. (ulcerative type): Due to:

- 1- Swallowing of sputum in open pulmonary T.B. (human type bacilli).
- 2- Reactivation of dormant intestinal lesion (bovine type bacilli).

Gross:

- T.B. ulcers in the ileocaecal region:
 - * Multiple and transverse (Fig.4.14).
 - * May be girdle shaped (involve the whole circumference).
 - * Undermined edges.
 - * Floor formed of caseation necrosis.
- Subserosal tubercles.
- Thickened peritoneum.

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Microscopic:

- Mucosa: **Ulcers** with undermined edges.
- Submucosa: **T.B. reaction** with massive caseation.
- **Subserous tubercles.**

Complications of T.B. enteritis

- 1- **T.B. peritonitis:** Rupture of subserosal tubercles without perforation.
- 2- **Suppurative peritonitis:** Due to perforation and secondary infection.
- 3- **Intestinal obstruction:** Due to healing by fibrosis with stricture formation.
- 4- **Blood spread.**
- 5- **Malabsorption:** Is postulated to be due to diminished absorptive surface due to ulceration and involvement of lymphatics and lymph nodes.



Fig.4.13: Typhoid ulcers.



Fig.4.14: Transverse TB ulcers of the ileum.

III. Malabsorption:

The term malabsorption is used to describe a number of clinical conditions in which one or more important nutrients are **inadequately absorbed by the gastrointestinal tract.**

Malabsorption results from disturbances in at least one of the four phases of nutrient absorption:

- 1- **Intraluminal digestion;** in which proteins, carbohydrates and fats are broken down into absorbable forms.
- 2- **Terminal digestion;** which involves the hydrolysis of carbohydrates and peptides by disaccharidases and peptidases respectively, in the brush border of the small intestinal mucosa.
- 3- **Transepithelial transport;** in which nutrients, fluid and electrolytes are transported across and processed within the small intestinal epithelium.
- 4- **Lymphatic transport** of absorbed liquids.

Table 4.2: Defects in malabsorptive diseases

Disease	Intra-luminal digestion	Terminal Digestion	Trans-epithelial Transport	Lymphatic transport
Celiac disease		+	+	
Tropical sprue		+	+	
Chronic pancreatitis	+			
Cystic fibrosis	+			
Disaccharidase deficiency		+		
Whipple disease				+
Acetalipo-proteinemia			+	
Parasitic gastroenteritis		+	+	
IBD	+	+	+	

Clinical picture of malabsorption syndrome:

1. The stools are bulky, full of fat, whitish, soft, frothy and of offensive odour due to excessive fermentation.
2. Abdominal distention.
3. Osteoporosis and rickets with low blood calcium leading to tetany.
4. Anaemia secondary to deficiency of iron, folic acid and/or vitamin B12.
5. Bleeding diathesis due to vitamin K deficiency.
6. Cachexia and failure to thrive.

Celiac disease:

- Also known as: Gluten-sensitive enteropathy or non tropical sprue.
- It is common in children.
- It is related to dietary gluten and represents an immune reaction to a constituent (gliadin) of this protein.
- Treatment of celiac disease is by gluten-free diet.

Microscopic: Villous atrophy, intraepithelial lymphocytic infiltrate and crypt hyperplasia.

Whipple disease:

- It is a rare systemic disorder in which men in the 3rd and 4th decades are most affected.
- Rod shaped bacilli are claimed in the pathogenesis of this disease.
- Defective T-lymphocyte function may predispose to infection by bacilli.

Tumours of the small intestine

A) Benign tumours:

1. **Adenomas:** These may arise from the small or large intestine. They will be discussed with tumours of the large intestine.
2. **Fibroma**, lipoma, and haemangioma are less frequent.

B) Malignant tumours:

1. **Adenocarcinoma:**

- It occurs in the **duodenum**, jejunum or **ampulla of Vater**.
- It is usually **annular**, therefore the symptoms are commonly those of **progressive intestinal obstruction**.
- **Obstructive jaundice** or **pancreatitis** may complicate the picture if the mass involves the ampulla of Vater.

2. **Primary lymphoma:**

- It is common in the small intestine.
- It **originates** in the **lymphoid follicles** of the **bowel wall**.
- The **classification** of **primary intestinal lymphoma** is **identical with that of nodal lymphoma**.

3. **Carcinoid tumour:**

It occurs in the **ileum** or **Meckel's diverticulum**. (See carcinoid tumour of appendix).

4. **GIST:** (See tumours of the stomach)

Diseases of the large intestine

Congenital anomalies:

1. Malrotations.
2. Reduplications of the colon.
3. Congenital megacolon (Hirschsprung's disease).

Congenital megacolon (Hirschsprung's disease):

It is a **familial disorder** in which **colonic dilatation** results from a **defect in the innervation of the rectum**.

Pathogenesis:

- It is due to **congenital absence** of **ganglion cells** in the **wall of the rectum**.
- **Arrested migration** of **neural crest cells** into the gut (**proximal to distal**) generates an **aganglionic distal colonic segment** with **functional obstruction** and **colonic dilatation proximal to the affected segment**.

Gross:

- The lesion always includes the **rectum** and may extend for a **variable distance proximally**.
- The **aganglionic rectum** and occasionally the **adjacent colon** are **permanently contracted**.
- The **proximal bowel** becomes **dilated** (Fig.4.15a&b).

Microscopic:

There is **transmural absence of ganglion cells** in the affected segment.

NB: Surgical excision of the aganglionic segment is the main line of treatment.

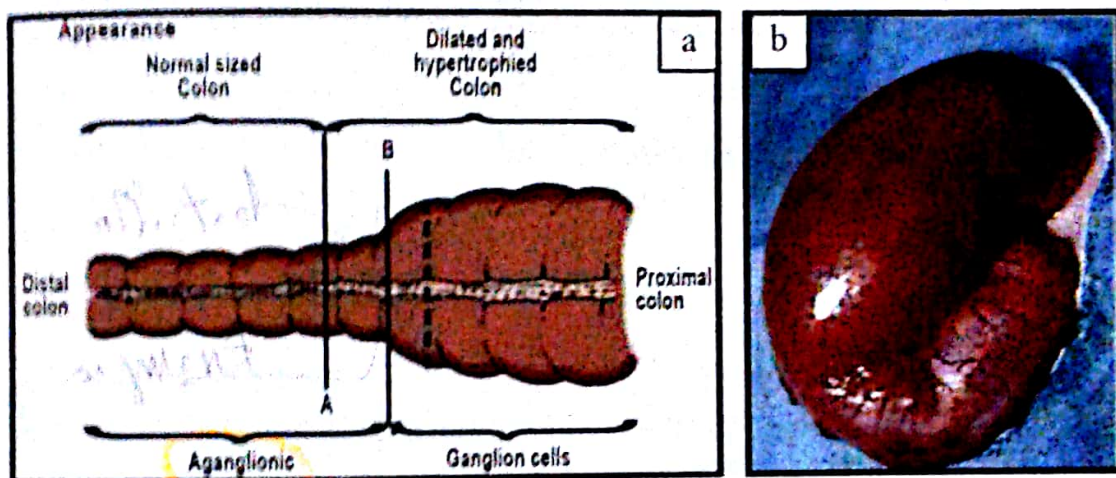


Fig.4.15: Hirschsprung's disease (a) Diagram.

(b) Gross

Inflammatory diseases:

A. Dysentery:

It is **characterized by diarrhea, tenesmus with passage of blood and mucus**.

Types of dysentery:

1- Bacillary dysentery:

Causes: The **schigella group of organisms** such as *Sch. schigae*, *Sch. flexner* and *Sch. sonnei*, which are gram negative bacilli.

Methods of infection: **Ingestion of the bacilli in contaminated food and fluids** or **transmitted by flies**.

Sites: It usually affects the **large intestine**, where **membranous inflammation** develops.

Gross: The **wall of the large intestine is thickened and oedematous, red and congested**. The **mucosa is usually necrosed and ulcerated**. It is **partially covered by thin greyish white pseudomembrane**.

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Microscopic:

The mucosa of the large intestine is nearly completely necrosed and is replaced by a pseudomembrane, formed of fibrin, necrotic tissue, many polymorphs and pus cells with some colonies of the organism. The submucosa is thickened, oedematous and markedly congested.

Complications:

1. Marked acute-toxaemia with its effects e.g. peripheral neuritis, acute toxic arthritis and toxic myocarditis.
2. Healing by fibrosis may lead to stenosis with chronic intestinal obstruction.
3. Perforation leading to acute suppurative peritonitis but this is very rare because the ulcers are superficial.

2- Amoebic dysentery or amoebiasis:

It is a very common disease in Egypt which occurs in all ages.

Causes:

- Entamoeba histolytica, ingested in contaminated food and milk.
- It is transmitted usually by flies from patients or carriers.
- The infection occurs by the cyst form of the parasite, which passes through the stomach unaffected by the gastric juice then hatches in the lower part of the small intestine where it divides and proliferates.
- The amoebae secrete proteolytic enzymes, leading to liquefactive necrosis of the colonic mucosa with the appearance of the characteristic amoebic ulcers.

Site:

The caecum is the commonest site then the ascending and transverse colons. In severe cases, the entire colon may be affected.

Gross:

- The colon shows multiple, small ulcers having undermined edges.
- They are deep and may reach even to the peritoneal surface.
- The mucous membrane inbetween the ulcers is usually intact.

Microscopic:

- The mucosa of the colon, shows multiple small ulcers with undermined edges and lined by necrotic tissues.
- Many amoebae are present in the wall and surrounded by small spaces.
- Secondary infection is common.

Fate:

Most of the cases recover completely with healing of the ulcers by regeneration of the mucosa.

Chapter 4: Diseases of the gastrointestinal tract

Complications of amoebic dysentery:

1. Chronic amoebic dysentery leading to a condition clinically known as spastic or irritable colon.
2. Perforation leads to acute suppurative peritonitis. This is rare but is usually fatal.
3. Healing by fibrosis may result in localized annular stricture.
4. Amoeboma: It is formed of chronic inflammatory mass with fibrosis and usually develops months and years after the original infection. The commonest site is the wall of the caecum and rectum, and may be mistaken for carcinoma or diverticulitis.
5. Amoebiasis of the liver.
6. Cutaneous amoebic lesions in the perianal region.
7. Bleeding per rectum which may be severe due to erosion of a large vessel.

3. Bilharzial dysentery; occurring with intestinal bilharziasis.

B. Inflammatory bowel disease (IBD):

It is a chronic condition resulting from inappropriate immune activation. IBD encompasses two diseases: Crohn's disease and ulcerative colitis.

Pathogenesis:

Several non confirmed factors are claimed as:

1. Genetic factors; mutations in certain genes regulating the immune response are found to be associated with Crohn's disease.
2. T-cell dysfunction; affecting mucosal immune response.
3. Epithelial defects; as abnormal Paneth cells in Crohn's disease.
4. Immune mediated damage; to the intestine, suggested by the chronic recurrent nature of the process and by the occurrence of systemic manifestation of autoimmune disease.

Crohn's disease:

This disease may affect the terminal ileum, ileocecal valve, cecum, colon or any part of the GIT.

Gross:

- 1) The affected bowel appears thickened and oedematous as does the adjacent mesentery.
- 2) The involved bowel segments are sharply demarcated and separated by normal areas "skip lesions". The cut surface of the bowel shows transmural thickening, oedema and fibrosis.

- 3) Cobble stone mucosa; due to nodular swelling, fibrosis and ulceration of the mucosa.
- 4) Fissure ulcers; deep linear defect or fissure (Fig.4.16).
- 5) The lumen is narrowed by oedema in early cases and by a combination of oedema and fibrosis in long standing diseases.
- 6) Mesenteric lymph nodes are frequently enlarged, firm and matted together.

Microscopic:

1. The disease appears as a chronic inflammatory process that extends through all layers of the bowel wall.
2. Fissure ulcers are seen together with mucosal and submucosal oedema (Fig.4.17).
3. The microscopic hallmark of Crohn's disease is the appearance of discrete, non-caseating granulomas, mostly in the submucosa.

Clinical picture:

- Mainly intermittent attacks of diarrhea, fever, abdominal pain, and weight loss, with intervening asymptomatic periods.
- Extra-intestinal manifestations include; uveitis, migratory polyarthritis and ankylosing spondylitis,

Complications:

- 1- Fibrotic strictures
- 2- Fistulas to adjacent viscera, abdominal and perineal skin, bladder or vagina.
- 3- Malabsorption.
- 4- Colonic bleeding and perforation.
- 5- The risk of intestinal cancer is increased in long-standing colonic Crohn's disease than normal population.

Ulcerative colitis:

It is limited to the colon and rectum (Table.4.3).

Gross:

- ❑ It involves the rectum and extends proximally to involve the entire colon (pancolitis).
- ❑ It is a disease of continuity with no skip lesions (Fig.4.16).

Chapter 4: Diseases of the gastrointestinal tract

- The mucosa may be:
 - Reddened, granular and friable with;
 - Inflammatory pseudopolyps, are isolated islands of regenerating mucosa that bulge into the lumen.
 - Extensive ulceration.
 - Or atrophic and flattened, this may lead to extreme dilatation "toxic megacolon" with a high risk of perforation.

Microscopic:

- Mucosal congestion, oedema, haemorrhages and diffuse inflammation of the lamina propria (inflammation is limited to the mucosa and submucosa).
- Ulceration, usually superficial.
- Crypt abscess appears as a dilated, degenerated crypt filled with neutrophils (Fig.4.18).
- Crypt distortion; it may appear tortuous, branched or shortened.
- Fibrosis is not prominent and strictures are absent.

Clinical:

- Intermittent attacks of bloody diarrhea, with expulsion of mucoid material, lower abdominal pain and cramps.
- Extraintestinal manifestations as; uveitis, migratory polyarthritis, pyoderma gangrenosa (necrotic skin lesion) and primary sclerosing cholangitis.

Complications:

- 1) Severe bleeding in the acute phase. ←
- 2) Toxic megacolon, characterized by dilatation of the colon with functional obstruction. ←
- 3) Rarely perforation. ←
- 4) Epithelial dysplasia with increased risk of colon cancer. ←

Table.4.3: Distinctive features of Crohn's disease and ulcerative colitis

Feature	Crohn's Disease	Ulcerative Colitis
Gross		
Bowel region	Ileum = colon	Colon only
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Bowel wall appearance	Thickened	Thin
Dilatation	No	Yes
Pseudopolyps	Mild to moderate	Marked
Microscopic		
Ulcers	Deep, linear (fissure)	Superficial
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	No
Granulomas	Yes (~35%)	No
Fistulas/sinuses	Yes	No
Clinical		
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Response to surgery	Poor	Good
Toxic megacolon	No	Yes

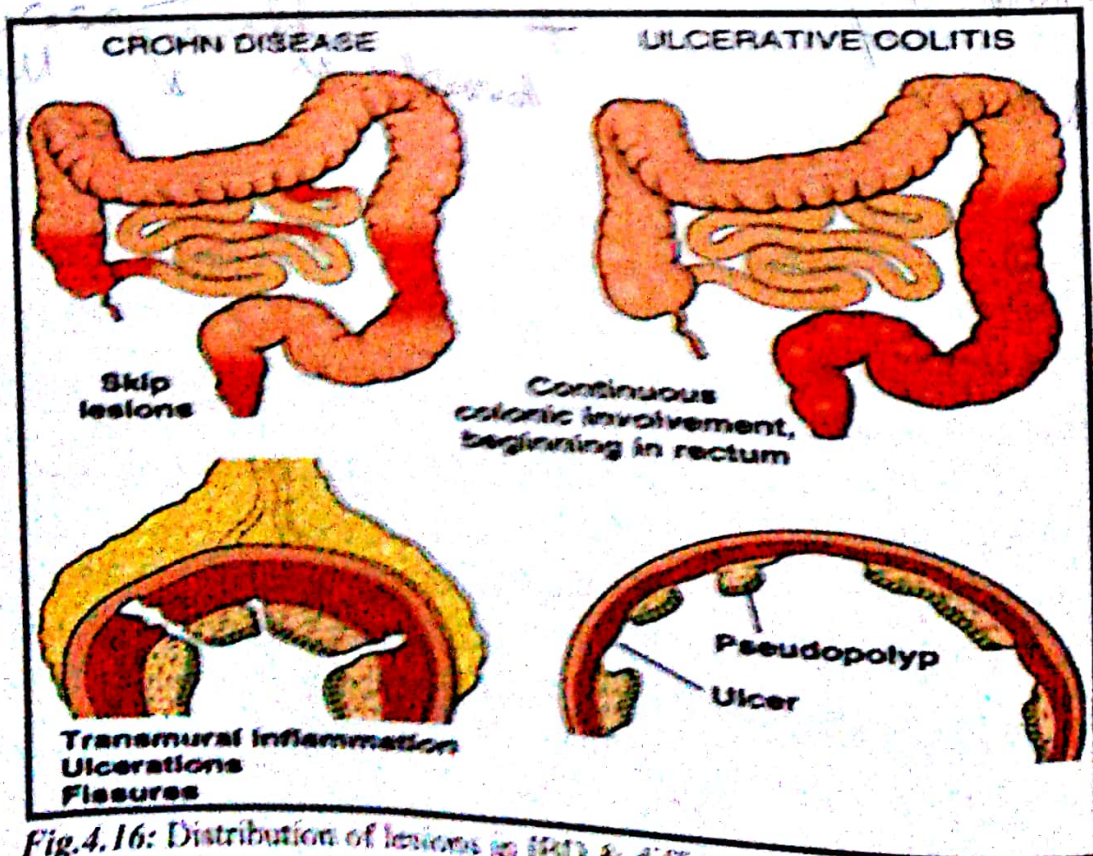


Fig.4.16: Distribution of lesions in IBD & differences



Fig.4.17: Crohn's disease, fissure ulcer



Fig.4.18: UC; Crypt abscess

Miscellaneous conditions:

a- Pseudomembranous colitis:-

It is, generally caused by *Clostridium difficile*, it is also known as antibiotic-associated colitis.

Risk factors

Antibiotic exposure, advanced age, hospitalization, and immunosuppression.

Morphology

The colon is coated by a tan pseudomembrane composed of neutrophils, dead epithelial cells and inflammatory debris.

Clinical Features

Fever, leukocytosis, abdominal pain, cramps, hypoalbuminemia, watery diarrhea, and dehydration.

b- Ischemic bowel disease:

Caused by acute or chronic hypoperfusion or infarction and it ranges from:

- *Mucosal infarction*; extending no deeper than the muscularis mucosa.
- *Mural infarction*; of mucosa and submucosa.
- *Transmural infarction*; involving all three layers of the wall.

c- Hemorrhoides:

Are tortuous dilated veins that protrude beneath the anal or rectal mucosa.

Risk Factors: Constipation, prolonged straining, pregnancy and portal hypertension.

Clinical: Pain and rectal bleeding of bright red blood.

Complications: They may become inflamed, thrombosed or ulcerated.

Diverticular disease:

It is an acquired herniation of the mucosa and submucosa through the muscular layers of the colon. *acquired*

- Diverticular disease is generally asymptomatic in 80% of the cases.
- Inflammation of these diverticulae is called diverticulitis.

Gross:

- They are generally multiple, small flask-like outpouchings.
- They appear in parallel rows between the mesenteric and lateral taeniae.

Microscopic:

- A diverticulum has a thin wall composed of flattened mucosa, compressed submucosa and attenuated muscularis mucosa.
- The wall of the diverticulum is in continuity with the surface mucosa.
- Fibrous thickening of colonic wall in chronic diverticulitis.

Complications:

1. Perforation and peritonitis rarely occurs.
2. Intestinal obstruction due to fibrosis in chronic diverticulitis.

Intestinal polyps:

1. Non neoplastic polyps:

- i) Bilharzial polyps: Common in Egypt.
- ii) Hyperplastic polyps. *small multiple with distal spread due to constipation*
- iii) Hamartomatous polyps:
 - a- Juvenile polyps (retention polyps): Common in children.
 - b- Peutz-Jegher's syndrome: It is a hereditary disorder characterized by intestinal polyps and mucocutaneous melanin pigmentation that carries an increased risk of several malignancies including cancer colon.
- iv) Inflammatory polyps: These may be seen in association with ulcerative colitis, infectious colitis or ischemic colitis.
- v) Lymphoid polyps: Submucosal accumulation of hyperplastic lymphoid tissue, almost in the rectum.

2. Neoplastic polyps: See tumours of large intestine.

Tumours of large intestine

A- Benign tumours:

1- Colorectal adenomas:

- Characterized by the presence of epithelial dysplasia.
- They are precursors of colonic cancer.

a. Adenomatous polyps:

- Tubular adenoma: They are small pedunculated polyps, composed of small, rounded or tubular glands (Fig. 4.19).
- Villous adenoma: They are often large and sessile, with a broad base and soft velvety papillary surface. It is composed of thin tall finger-like processes lined by epithelial cells and supported by a fibrovascular cores (Fig. 4.20).
- Tubulovillous adenoma: It has a mixture of both tubular and villous features.

Risk factors in adenoma:

- Size of the adenoma: is the most important characteristic that correlates with risk of malignancy (The risk increases with larger size)
- Grade of dysplasia: Either low or high-grade dysplasia.

b. Familial adenomatous polyposis (polyposis coli):

- ❑ It is an autosomal dominant syndrome exhibiting innumerable adenomatous polyps in the colon. A minimum of 100 colonic adenomas are required for diagnosis (Fig. 4.21).
- ❑ It is caused by mutation of APC suppressor gene.
- ❑ The risk of progression to adenocarcinoma is virtually 100%, and prophylactic colectomy is curative.
- ❑ Polypi are mostly tubular adenoma, though tubulovillous and villous types may be present.

Complications of neoplastic polyps:

1. Ulceration and bleeding.
2. Intussusception.
3. Malignant transformation.

2. Mesenchymal tumours: GIST, neurilemmoma, lipoma and hemangioma.

B- Malignant tumours:

1. Adenocarcinoma:

Pathogenesis:

- The peak age incidence at 60-70 years.

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- More common in males than females
- Diet: Low vegetable fiber intake, high content of refined carbohydrates and high fat content increase the risk of cancer.
- Pre-existing adenoma and ulcerative colitis.
- Genetic factors:
 - Adenoma-carcinoma sequence: inherited mutation of APC gene, followed by mutation of K-RAS, and P53.
 - Microsatellite instability pathway; in patients with defects in DNA mismatch repair genes (Hereditary non polyposis colon cancer).

Gross: It may be;

- Polypoid fungating mass in proximal colon.
- Annular encircling mass (napkin ring) in distal colon.
- Or may present as a malignant ulcer (Fig.4.22).

Microscopic variants:

- Adenocarcinoma (Fig.4.23).
- Mucoid carcinoma (Fig.4.24).
- Signet-ring cell carcinoma.

Clinical:

- Occult bleeding is detected via a fecal occult blood test.
- Intestinal obstruction.
- Abdominal pain.
- Fatigue and weakness from iron deficiency anaemia.
- Changes in bowel habits.
- Symptoms of metastasis.

Spread:

- Local spread into the wall of the intestine and the surrounding tissue.
- Lymphatic spread to regional lymph nodes.
- Krukenberg tumor.
- Blood spread to the liver, lungs, bones and brain.

Prognosis: Depends on the depth of invasion and lymph node metastases (Table.4.3 & Fig.4.25).

- II. Carcinoid tumour and lymphomas; are less frequent in the large intestine than in the small intestine.
- III. Squamous cell carcinoma; occurs in the anal canal.
- IV. Malignant melanoma; occurs rarely in the anus.
- V. Malignant GIST.

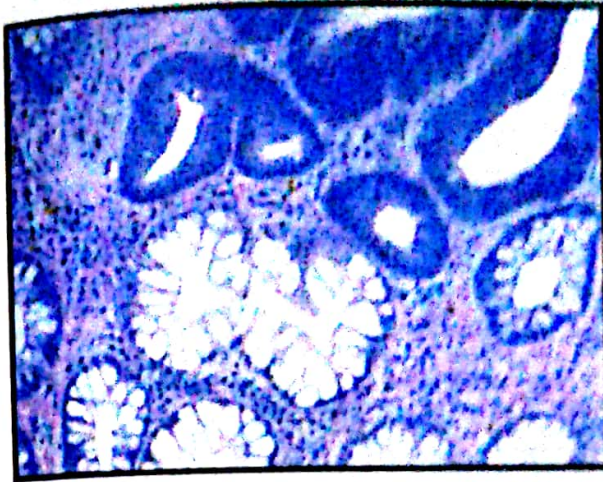


Fig.4.19: Tubular adenomatous polyp

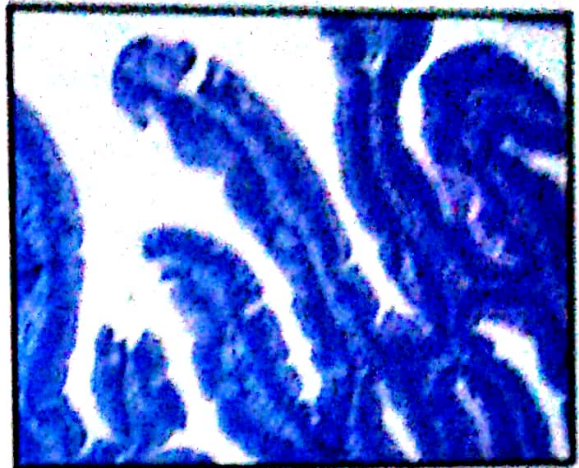


Fig.4.20: Villous adenoma

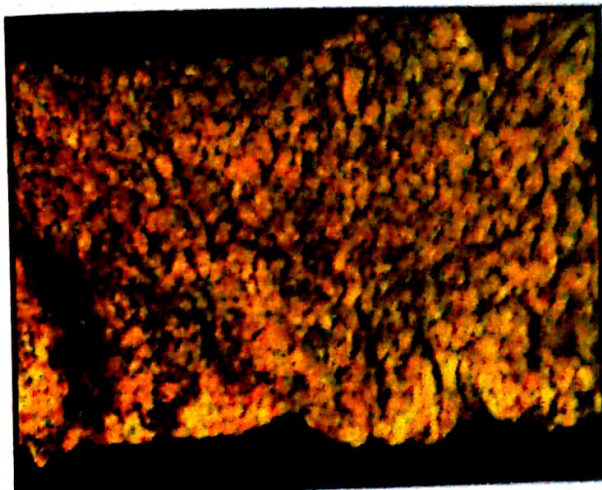


Fig.4.21: Familial polyposis coli



Fig.4.22: Colonic malignant ulcer

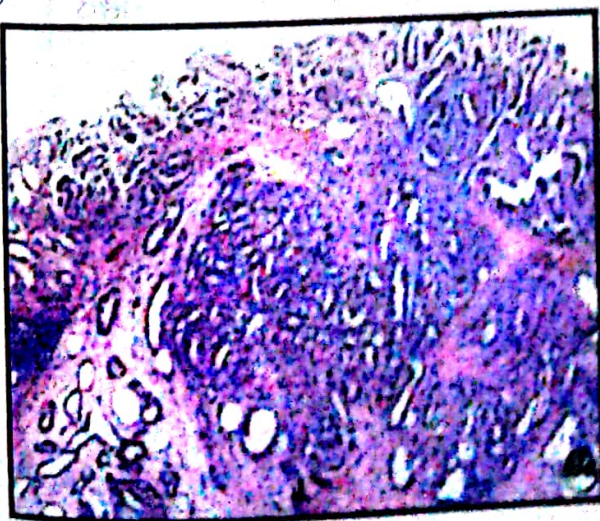


Fig.4.23: Colonic adenocarcinoma

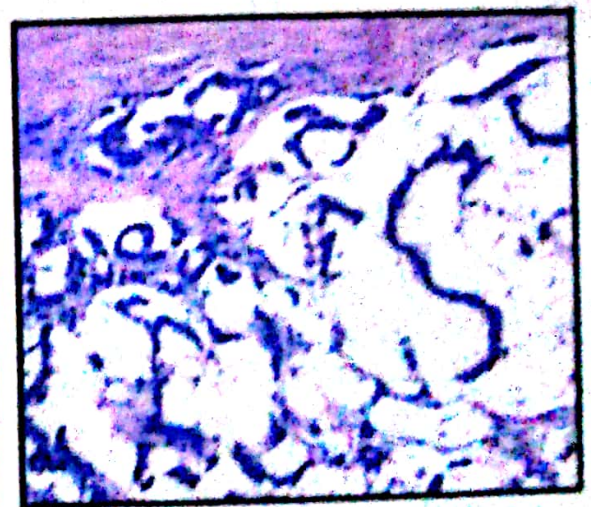


Fig.4.24: Colonic mucoid adenocarcinoma

Chapter 4: Diseases of the gastrointestinal tract

Table 4.3: TNM classification of colorectal cancer

Designation	Description
Tumor	
Tis	In situ carcinoma
T1	Tumor invades the submucosa
T2	Tumor invades, but not through muscularis propria
T3	Tumor invades through muscularis propria
T4	Tumor invades the adjacent organs or visceral peritoneum
Regional lymph nodes	
Nx	Lymph nodes can not be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in 1 - 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
Distant metastasis	
MX	Distant metastasis can not be assessed
M0	No distant metastasis
M1	Distant metastasis or seeding of abdominal organs

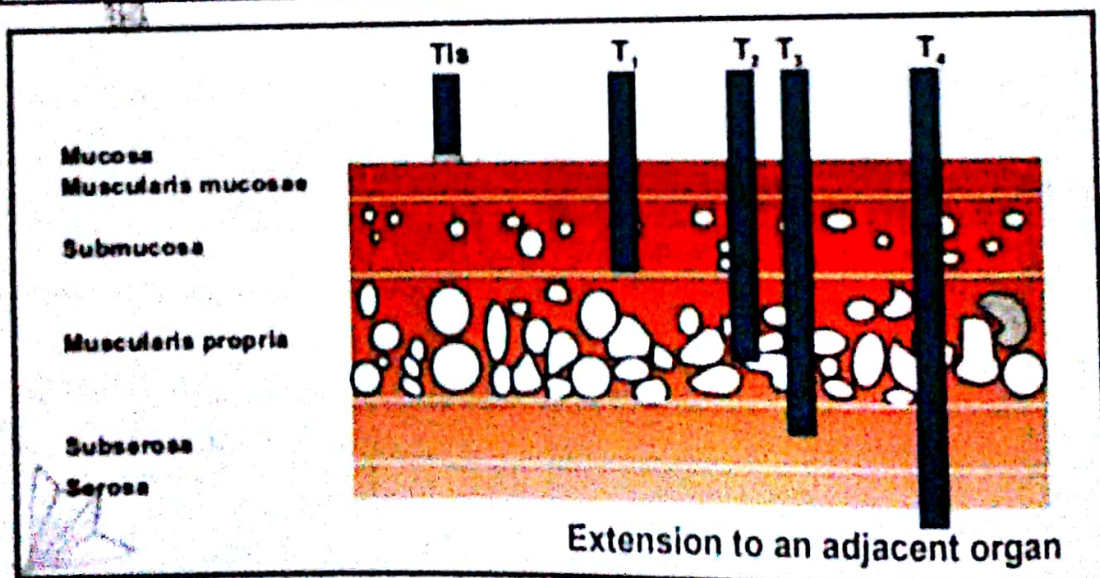


Fig.4.25: Staging of colorectal carcinoma

Intestinal obstruction: It may be acute or chronic.

A- Acute intestinal obstruction:—

It is complete obstruction to the passage of faeces and gases.

Causes:

1. **Intraluminal causes:** are not common. The lumen of the large bowel, is usually obstructed by; **impaction of a hard faecal mass or a faecolith**, a **ball of ascaris worms**, a large gall stone and inspissated meconium in a newborn.

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2. **Intussusception:** It is the invagination of a loop of intestine into another part. It occurs more commonly in children than in adults. (Fig.4.26a).

Causes:

- In children:** It may be due to over-intake of fluids, Meckel's diverticulum and hyperplasia of the lymphoid tissue at the ileocecal valve.
- In adults:** It may be due to a swallowed foreign body, polypoid tumours of mucosa as adenoma and carcinoid tumour or may be due to Meckel's diverticulum.

Site: The usual site is at the ileo-cecal valve i.e. ileo-cecal intussusception. Ileo-ileal intussusception is less common. Colocolic and sigmoido-rectal intussusception are very rare.

3. **Strangulated hernia:** It occurs when a loop of intestine is forced through an opening in the abdomen e.g. inguinal opening accompanied by increase of pressure in the hernial sac due to accumulation of gas or faeces. The sharp edges of the neck of the hernia interfere with the venous return causing further swelling of the loop which increases the amount of strangulation leading to acute intestinal obstruction (Fig.4.26b).

4. **Volvulus:** It is the twisting of a loop of intestine with obstruction of its lumen and the mesenteric vessels (Fig.4.26c).

The usual causes are; bands, adhesions and long mesentery.

The commonest site is in the sigmoid colon.

5. **Paralytic ileus:** There is complete cessation of the peristaltic movements which results in intestinal obstruction.

The usual exciting cause is post-operative complication with much trauma to the intestines or pelvic peritonitis complicating acute suppurative appendicitis in which a loop of ileum hangs down into the pus and becomes completely paralysed.

6. **Mesenteric vascular occlusion:** It results in cut of blood supply to a loop of intestine, followed by red or haemorrhagic infarction, moist gangrene and acute intestinal obstruction.

It is due to thrombosis in an atherosclerotic mesenteric artery or embolism.

Effects of acute intestinal obstruction:

- Severe abdominal colicky pain, distension and vomiting.
- Haemorrhagic infarction followed by gangrene of the affected segment. Above the obstruction, the intestine is distended while below the obstruction it is collapsed.

3. **Marked loss of fluids** with dehydration and disturbed electrolyte balance.
4. **Renal failure.**
5. **Shock** is the end result which is rapidly fatal.

B- Chronic intestinal obstruction:

Causes:

1. Causes in the walls:
 - a- **Carcinoma of colon**; particularly infiltrating types.
 - b- **Healing of intestinal ulcers**; as amoebic, tuberculous and Crohn's disease.
 - c- **Ischaemic stricture**; complicating ischaemic colitis is usually annular.
 - d- **Adhesions between loops of intestine**; as in tuberculous peritonitis or as a post-operative complication.
 - e- **Megacolon**; as in congenital or toxic megacolon.
2. **Pressure from outside**: By a large ovarian cyst or a big **uterine leiomyoma**.

Effects of chronic intestinal obstruction:

1. **Hypertrophy and dilatation of the wall**, proximal to the site of obstruction.
2. **The intestine below the obstruction is usually collapsed.**
3. **Hard faecal masses may accumulate above the obstruction**, leading to ulceration of the mucosa known as **stercoral ulcers**.
4. **Acute on top of chronic intestinal obstruction may occur due to impaction of a hard faecal mass** or due to local inflammatory oedema.

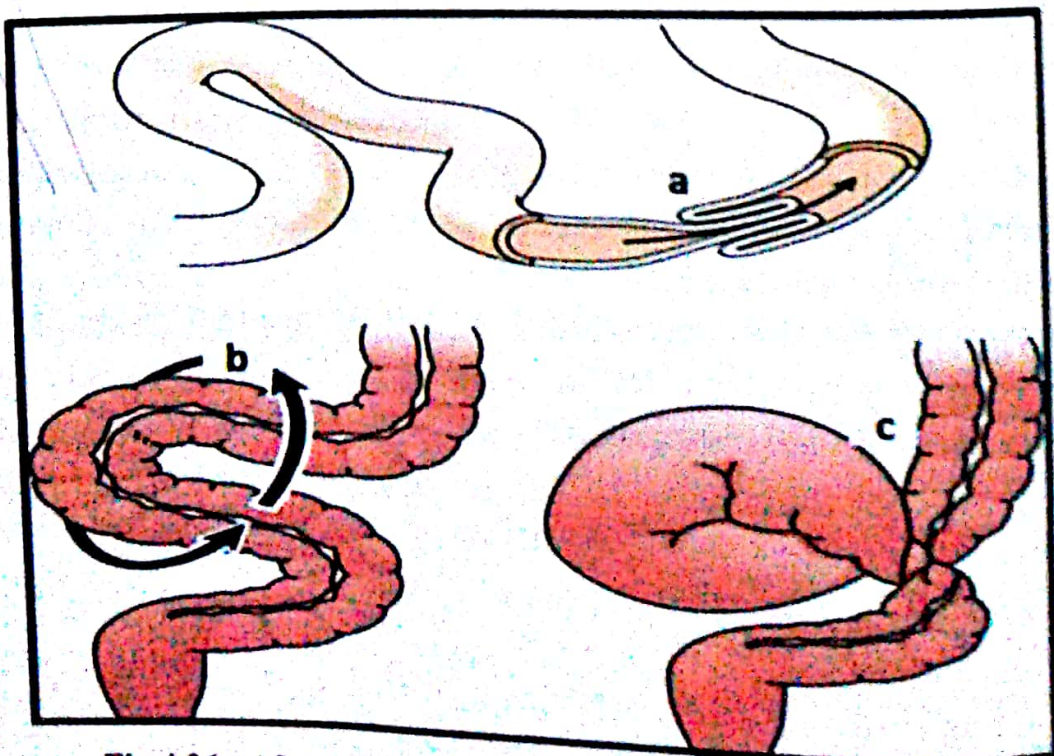


Fig. 4.26: a) Intussusception, b) Volvulus, c) Adhesions.

Diseases of the appendix

The appendix is a normal diverticulum of the cecum.

Appendicitis:

It is inflammation of the appendix that may be acute or chronic.

Acute appendicitis:

It is more common in males in the second and third decades and is very rare before the age of 5 years.

Pathogenesis:

- a- Obstruction of the lumen of the appendix that interferes with the normal peristaltic drainage due to
 - Foreign material especially food residues and seeds of fruits, which become surrounded by faecal material to form faecolith.
 - Less commonly gall stone, tumour or mass of worms.
- b- Ischemic injury and stasis of luminal contents favour bacterial proliferation, trigger inflammatory responses.

Gross:

1. Acute catarrhal appendicitis:
 - o It represents the early stage of the disease.
 - o The appendix is slightly swollen, congested with dull granular serosa.
2. Acute suppurative appendicitis:
 - ♦ The serosa is covered by fibrinopurulent exudate (Fig.4.27).
 - ♦ On opening the appendix, the lumen is filled with purulent exudates, focal abscesses may form within the wall.
 - ♦ The mucosa may show focal ulcerations and faecolith may be noted
3. Acute gangrenous appendicitis:
 - ♦ Starting usually at the tip
 - ♦ The wall becomes soft and friable and the surface is coated with greenish-black gangrenous necrosis (Fig.4.28).
 - ♦ The mucosa is ulcerated.

Microscopic:

- The lumen is usually filled with necrotic material with many polymorphs and pus cells.
- The mucosa may show areas of ulcerations, with hyperplasia of the lymphoid tissue.
- There is marked infiltration of the wall by polymorphs and pus cells.
- The subserosa is oedematous, congested and covered by suppurative exudate.

Effects and complications:

1. **Perforation:** with acute generalized suppurative peritonitis.
2. **Appendicular mass:** Is a mass of inflamed tissue located in the right lower quadrant, which surrounds an acutely inflamed and/or ruptured appendix with appendicitis.
3. **Appendicular abscess:** It is due to rupture of an appendix giving rise to localized abscess in the right iliac fossa. This abscess may spread to other sites as between the liver and diaphragm "subphrenic abscess.
4. **Septic thrombophlebitis of the appendicular veins:** May develop and leads to portal pyaemia.
5. **Fistulous formation:** It is rare and may develop when an appendicular mass or abscess ruptures into the anterior abdominal wall or the urinary bladder.

Mucocele of the appendix:

It is a rare condition in which the lumen is distended with mucus, the wall is thin and the mucosa is flattened (Fig.4.29).

- It usually follows acute appendicitis with obstruction of the lumen.
- It may be a consequence of mucinous cystadenoma or mucinous cystadenocarcinoma.
- Secondary infection results in the formation of empyema of the appendix.

Tumours of the appendix

Tumours of the appendix are very rare.

Benign tumours:**1. Carcinoid tumour:**

- Incidence peaks at ages 20-39 years.
- The commonest site is the appendix.
- It arises from the argentaffin cells which are found throughout the gastrointestinal tract but are more numerous in the appendix.
- The ileum is the next frequent site followed by rectum and colon.

Gross:

It is mostly situated at the tip, and appears as a circumscribed yellowish nodule usually less than 1cm (Fig.4.30).

Microscopic:

- Tumours arise in mucosa; infiltrate the mucosa, submucosa and the muscularis propria
- The neoplastic cells are uniform, polygonal with granular eosinophilic cytoplasm arranged in nests, acini or insular pattern.

Clinical:

- Carcinoid tumours typically grow very slowly. Nodal and distant spread are exceptionally rare.
- Carcinoid syndrome. Occurs in tumours metastasizing to the liver, and it is due to secretion of 5-hydroxytryptamine or serotonin by the tumour cells. The patient suffers from attacks of flushing, watery diarrhea and dyspnea resembling that of bronchial asthma.

2. Mucinous cystadenoma.

Malignant tumours:

Carcinoma of the appendix is very rare and is usually adenocarcinoma or mucinous cystadenocarcinoma.

NB: *Pseudomyxoma peritonii* may complicate mucinous tumours of the appendix (See tumors of the ovary).



Fig.4.27: Acute suppurative appendicitis



Fig.4.28: Acute gangrenous appendicitis

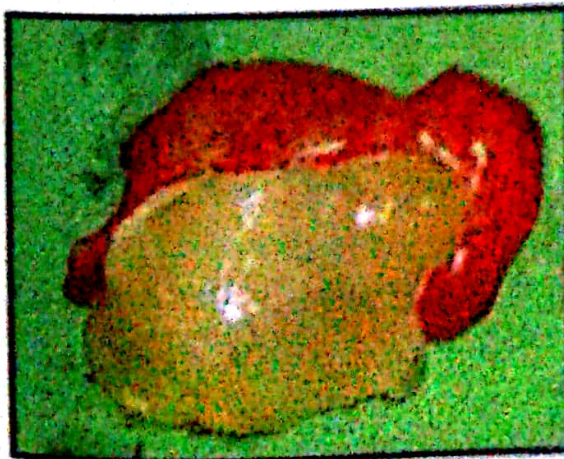


Fig.4.29: Mucocoele of the appendix



Fig.4.30: Carcinoid tumour of the appendix

Summary

Diseases of the oral cavity:

Stomatitis: Aphthous stomatitis, herpetic stomatitis, agranulocytous angina, candidiasis, syphilis of the mouth. Leukoplakia and erythroplakia.

Tumours: Squamous papilloma, haemangioma, squamous cell carcinoma.

Diseases of the salivary glands:

Sialadenitis: Mumps, bacterial sialadenitis, Sjogren's syndrome.

Tumours: benign: Pleomorphic adenoma, papillary cystadenoma lymphomatousum. Malignant: Mucoepidermoid, adenoidcystic, undifferentiated carcinoma & carcinoma in pleomorphic adenoma.

Diseases of the pharynx:

Tumours: Squamous cell papilloma, squamous cell carcinoma.

Diseases of the oesophagus:

Oesophageal varices:

Oesophagitis: Reflux oesophagitis, Barrett's oesophagus.

Tumours: Squamous cell carcinoma, adenocarcinoma.

Diseases of the stomach:

Chronic gastritis: Helicobacter pylori, autoimmune & reactive gastritis.

Peptic ulcer disease.

Gastric Polyps: Inflammatory, hyperplastic & fundic gland polyps.

Tumours: Gastric adenoma, carcinoma, lymphoma, carcinoid tumor & (GIST).

Diseases of the small intestine:

Typhoid fever, Tuberculous enteritis.

Malabsorption: Coeliac & Whipple Disease.

Tumours of the small intestine: Adenomas, adenocarcinoma, lymphoma, Carcinoid & GIST.

Diseases of the large intestine:

Congenital megacolon (Hirschsprung's disease).

Bacillary, amoebic Dysentery bilharzial.

Inflammatory bowel disease: Crohn's disease & ulcerative colitis.

Intestinal polyps: Bilharzial, hyperplastic & hamartomatous.

Tumours: Adenomas, familial adenomatous polyposis, adenocarcinoma, carcinoid, malignant melanoma & malignant (GIST).

Diseases of the appendix: Acute appendicitis

Tumours: Carcinoid tumour, mucinous cystadenoma, adenocarcinoma and mucinous cystadenocarcinoma.

Chapter 5

Intended Learning Outcomes (ILOs):

By the end of this unit the students will be able to:

- ☐ Describe the morphologic features acute and chronic viral hepatitis, list fate and complications.
- ☐ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.
- ☐ Identify types of hepatitis and the characteristic pathologic feature of each.
- ☐ Define cirrhosis, list its types, and describe its pathologic features and clinical course.
- ☐ Compare and contrast between primary and secondary biliary cirrhosis.
- ☐ Compare and contrast between suppurative and amoebic liver abscesses.
- ☐ Classify tumours of the liver, list the precancerous factors and describe the pathologic features of hepatocellular carcinoma.
- ☐ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and / or laboratory findings.
- ☐ Define jaundice, list its types and explain pathogenesis.
- ☐ Define cholecystitis. Explain the pathogenesis and describe the pathologic features of acute and chronic cholecystitis.
- ☐ Compare and contrast between pigmented and cholesterol stones.
- ☐ Classify tumours of the gall bladder, list the precancerous factors and describe the pathologic features.

DISEASES OF THE LIVER

Micro-anatomy of the liver:

The liver consists of either acini or lobules (*Fig.5.1*).

- **Acini** are centered around the axial vessels emanating from the hepatic artery and portal vein in the adjacent portal tracts. The periphery is demarcated by the surrounding hepatic veins.

The hepatic acinus is subdivided into 3 zones:

- **Zone 1** is the nearest to the axial vessels in the portal tract. It is the most rich in the blood supply!
- **Zone 2** lies between zones 1 & 3!
- **Zone 3** lies around the central vein with the least blood supply!
- **Lobules** are centered around central veins. Their periphery is demarcated by imaginary lines joining each of the surrounding portal tracts. It is subdivided into **centrizonal**, **midzonal**, and **periportal**!

Types of necrosis of the liver:

1. Hepatocyte necrosis:

- a- **Cytolysis:** Rupture of cell membrane of swollen degenerated cell (ballooning degeneration) leads to dropout hepatocyte.
- b- **Apoptosis:** in which hepatocytes shrink, become intensely eosinophilic and have fragmented nuclei. When located in the parenchyma away from portal tracts are called **spotty necrosis** or **lobular activity** (*Fig.5.2*).

2. Zonal necrosis:

It is necrosis is limited to a certain zone of the hepatic acinus e.g. necrosis develops in zone (3) in acute and chronic viral hepatitis, chronic venous congestion and in paracetamol and carbon tetrachloride toxicity.

3. Piece-meal necrosis (Interface Hepatitis):

The necrosis is located at the interface between liver parenchyma and portal tract (or scar when present).

The lymphocytes in the portal tracts spillover into adjacent parenchyma and surround the necrotic hepatocytes (*Fig.5.3*).

Its presence denotes **progressive liver damage (activity)**.

4. Confluent necrosis: In severe cases the necrosis is seen around the central vein.

5. Bridging necrosis (Fig 3.4) It means necrosis which links two portal tracts i.e. portal-portal bridging necrosis (P-P) or portal tract and central vein, i.e. portal-central bridging necrosis (P-C).
6. Submassive and massive hepatic necrosis
 - a- Submassive necrosis. The necrosis affects the entire liver lobule or groups of adjacent lobules.
 - b- Massive hepatic necrosis Multilobular necrosis affecting almost all the liver, it is rare and invariably fatal.

Causes: Severe viral hepatitis, autoimmune hepatitis, drug reactions or toxic injury.

Clinical: Both present with fulminant hepatitis and liver cell failure (Cholemia).

Viral hepatitis

Viral hepatitis usually refers to infection of the liver tissue by one of the "hepatotropic viruses" (Table 5.1)

1. Hepatitis A:

- It is caused by (HAV), RNA virus
- It is transmitted by fecal-oral route
- The incubation period varies from 15 - 45 days
- It is a self limited disease, it does not turn to chronic condition
- No carrier state and infection leads to long life immunity

2. Hepatitis B:-

- It is caused by HBV, DNA virus
- The incubation period varies from 50 - 180 days
- The virus is not directly cytopathic and the liver cell injury depends on the cell mediated immune response of the individual.
- It is responsible for many cases of chronic carrier, fulminant hepatitis with massive liver necrosis, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma.

Methods of infection by HBV:

1. Hepatitis B is primarily parentally transmitted through transfusion of blood or the use of contaminated syringes
2. Non-parental transmission. If infected blood comes in contact with minor abrasions e.g., razors at barber shops, or during surgical operations. Also by using contaminated instruments

Chapter 5: Diseases of the liver

3. Vertical transmission: During childbirth.
4. All body fluids are potentially infectious: Saliva, semen, CSF, pleural and peritoneal fluids.
5. Sexual contact is a well known route of transmission in homosexuals.

Hepatitis C:

- It is caused by HCV which is a parenterally transmitted.
- The clinical course and mode of transmission are similar to those of hepatitis B, but **sexual transmission is not yet settled**.
- The incubation period ranges from 15 - 150 days.
- **Chronic liver disease** is a more frequent complication than in hepatitis B and cirrhosis occurs in high percentage of cases.
- Also it has a role in the pathogenesis of **hepatocellular carcinoma**.

Hepatitis D:

- It is caused by HDV or "Delta virus" which is RNA defective or incomplete virus. It affects only those with hepatitis B infection as it needs HBV for its replication.
- The incubation period ranges from 50 - 180 days.
- It is **parenterally transmitted**.

HDV infection occurs either simultaneously with HBV "co-infection" or following HBV infection "super infection".

- Most **coinfecting** persons recover completely.
- While in most **superinfected** persons there is acceleration of hepatitis, progressing to more **severe chronic hepatitis** in 4-7 weeks.

Hepatitis E:

- It is RNA virus resembling HAV.
- It is transmitted by the fecal-oral route.
- The incubation period is from 15 - 160 days.
- The virus causes a self limited hepatitis with no chronicity or **carrier state**.

NB: A large number of (non hepatotropic) viruses can also affect the liver such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV) and yellow fever virus.

Clinical features of acute viral hepatitis:

- ❑ **Preicteric phase:** Anorexia, nausea, vomiting, low grade fever.
- ❑ **Icteric phase:** Jaundice and passage of dark urine and pale stool.
- ❑ Some patients with HBV may present with **fever, rash and arthralgia**.

Table 5.7: Clinical features and outcome of hepatotropic viruses

	HAV	HBV	HCV	HDV	HEV
1. Type of virus	RNA	DNA	RNA	RNA	RNA
2. Incubation period	2-6 weeks	4-26 weeks	2-26 weeks	4-26 weeks	2-8 weeks
3. Method of transmission	Faecal-oral	Parenteral & Sexual	Parenteral	Parenteral	Faecaloral
4. Progression to chronicity	Never	10%	80%	5% coinfection 70% superinfection	Never
5. Carrier state	Never	±	+	+	No
6. Cirrhosis and hepatocellular carcinoma	No	± Occur	± occur in higher % of cases	± Occur	No

Morphology of acute viral hepatitis:

Gross: The liver is mildly enlarged and reddened or greenish if cholestatic.

Microscopic:

1- Hepatocyte injury:

○ **Ballooning degeneration** (hydropic change): Swollen hepatocytes with indistinct cell membrane and pale granular cytoplasm (Fig. 5.5).

○ **Cholestasis:** Intracellular accumulation of bile pigment.

○ **Mild fatty change** of hepatocytes.

○ **Hepatocyte necrosis** of isolated cells or clusters:

a- **Lytic necrosis, apoptosis** (Fig. 5.6), **lobular activity**

b- **If severe bridging necrosis** may occur.

c- **Lobular disarray** loss of architecture (Fig. 5.7).

2- **Reactive changes:** Hepatocyte proliferation (regeneration).

3. **Sinusoidal cell reactive changes:** Accumulation of phagocytosed cellular debris in **Kupffer cells**.

4 **Portal tracks:** Show mononuclear inflammatory cell infiltrate.

Interface hepatitis may occur in severe cases.

Fate and sequelae of acute viral hepatitis:

1. **Recovery:** is the usual outcome in all cases of HAV & HEV; in 90% in cases of HBV and in 20 - 30% of cases of HCV.

2. **Fulminant hepatitis:** which is fatal in less than 1% due to massive hepatic necrosis.

3. **Chronic carrier state:** it refers to an individual without manifest symptoms, who harbors and therefore can transmit the virus.

4. **Chronic hepatitis:**

- It occurs in 10% of HBV and in 40 - 60% of patients with HCV.
- It may progress to cirrhosis in about 20% of the patients.
- Hepatocellular carcinoma develops as a complication of chronic hepatitis and cirrhosis in some patients with HBV & HCV.

Chronic hepatitis:

It is defined as: persistence of symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than six months with histologically documented inflammation and necrosis.

Microscopic features of chronic hepatitis

1- In addition to those of acute hepatitis, there are:

2- **Portal tracts:**

➤ **Inflammation:**

- Confined to portal tracts; mononuclear inflammatory cell. Lymphoid aggregates may be seen in HCV.
- **Piece-meal necrosis (Interface hepatitis).**
- **Bridging inflammation and necrosis.**

➤ **Fibrosis:** it is the hallmark of serious irreversible liver damage.

- Portal.
- Portal and periportal fibrosis.
- Bridging fibrous septa.

NB: These microscopic features may be present in other types of chronic hepatitis.

Specific features of HCV:

- Fatty change of hepatocytes.
- Lymphoid infiltrates in portal tracts, sometimes with lymphoid follicles.
- Bile duct injury (Fig. 5.8).

Specific features of HBV:

- □ Ground glass hepatocytes due to accumulation of HbsAg in the cytoplasm (Fig. 5.9).

The viral particles can be detected by orcein stain or by immunohistochemical staining.

Grading and staging of hepatitis (Modified Knodell's score) is done for therapeutic implications.

1. **The Grade (Degree of disease activity)** is graded from (1-4).
It depends on the extent of portal tract inflammation, piecemeal necrosis, spotty and bridging necrosis.
2. **The stage (degree of scarring)**: is graded from (1-4).
For each case a numerical score for grade and stage is defined.
The greater the score the greater the risk for progression to cirrhosis.

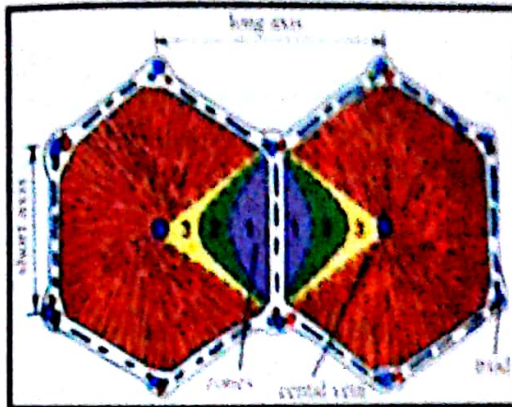


Fig.5.1: Liver acini & lobules.

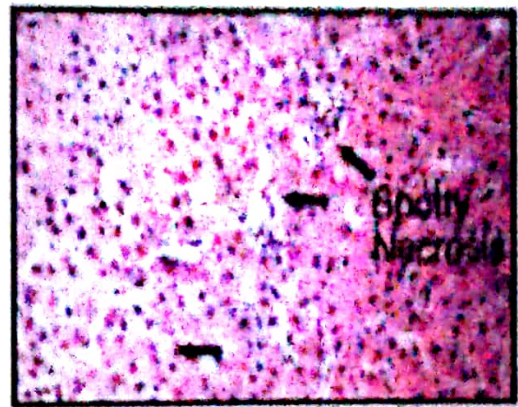


Fig.5.2: Acute viral hepatitis, spotty necrosis.

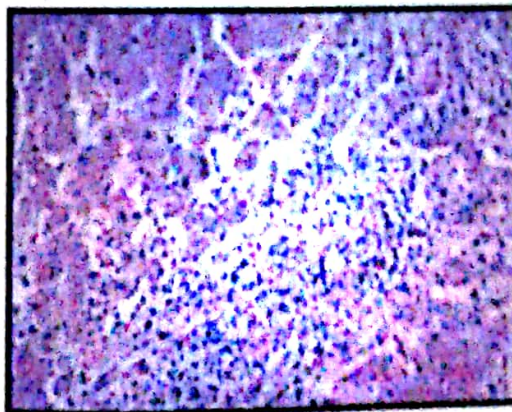


Fig.5.3: Interface hepatitis.

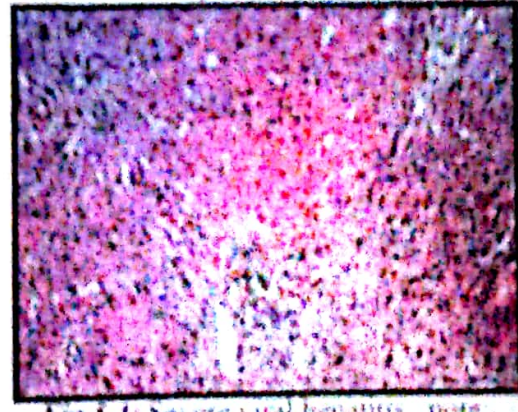


Fig.5.4: Severe viral hepatitis, note bridging necrosis.

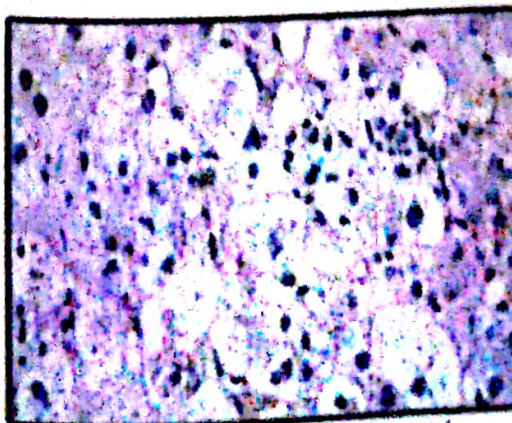
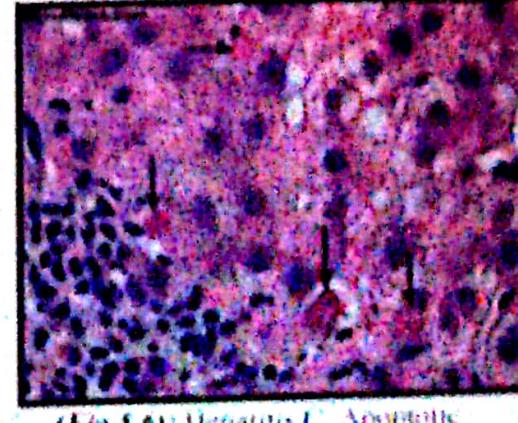


Fig.5.6: Acute hepatitis B, with ballooning degeneration.



(Fig.5.6): Hepatitis C, Apoptotic cells (arrows).

Other causes of chronic hepatitis are:

1. Autoimmune hepatitis:

- In this condition autoantibodies are produced against hepatocytes.
- Most patients are positive for smooth muscle antibody (SMA) and antinuclear antibodies (ANA) and are negative for antimitochondrial antibody (AMA).
- There is elevated serum IgG levels.
- There is female predominance (70%).

Microscopic:

- Severe chronic hepatitis with widespread confluent necrosis.
- Marked inflammation and fibrosis.
- Infiltration by clusters of plasma cells, (Fig. 5.10).

2. Alcoholic hepatitis:

It is characterized microscopically by (Fig. 5.11):

- ❑ Fatty change, typically begins in centrilobular hepatocytes.
- ❑ Hepatocyte ballooning swelling and necrosis, especially in zone (3).
- ❑ Neutrophilic reaction around injured hepatocytes.
- ❑ Mallory's bodies, eosinophilic cytoplasmic inclusion in degenerated hepatocytes.
- ❑ Fibrosis starts perivenular and ends in micronodular cirrhosis.

3. Drug-induced hepatitis:

At least 10% of drug reactions involve the liver, because it has a central role in metabolism, conjugation and elimination of toxic substances from the body. *It is characterized microscopically by:*

- Fatty change and necrosis especially in zone (3).
- Cholestasis.
- Mixed inflammatory infiltrate rich in eosinophils with fibrosis.
- Non caseating epithelioid granuloma may be noted.

4. Wilson disease:

- It is a rare but treatable inherited disorder in which copper accumulates in the liver and in basal ganglia of the brain.
- The underlying defect is failure of the liver to excrete copper in the bile.

Microscopic:

- Chronic hepatitis ending in cirrhosis.
- Orcein stain shows dark brownish granules of copper in the hepatocytes (Fig. 5.12).

Chapter 5: Diseases of the liver

Clinical: Hepatic and neurological abnormalities

- Kayser-Fleischer (brown) rings at the corneal limbus.
- Diagnosis is confirmed by finding a low concentration of ceruloplasmin (a copper containing protein) in blood.



Fig.5.7: Acute hepatitis B, Lobular disarray & bile plugs.

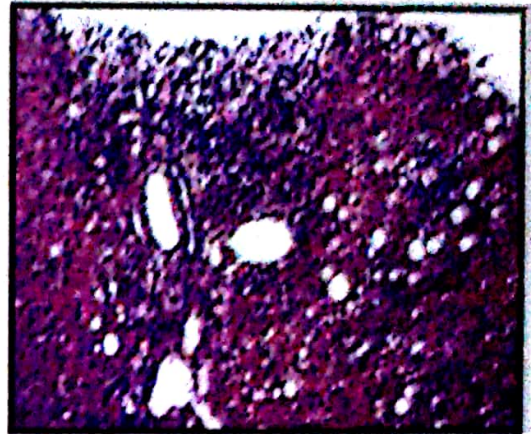
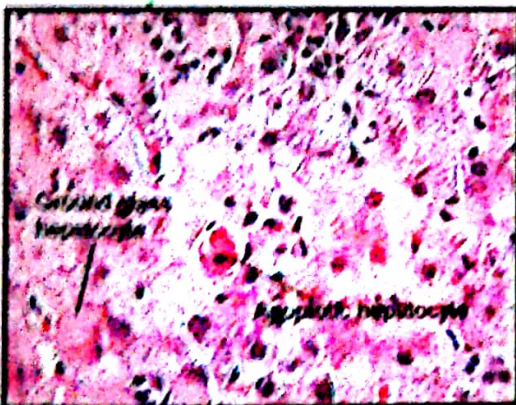


Fig.5.8: HCV (lymphocytes & steatosis).



(Fig.5.9): HBV (ground glass hepatocytes) with apoptotic body.

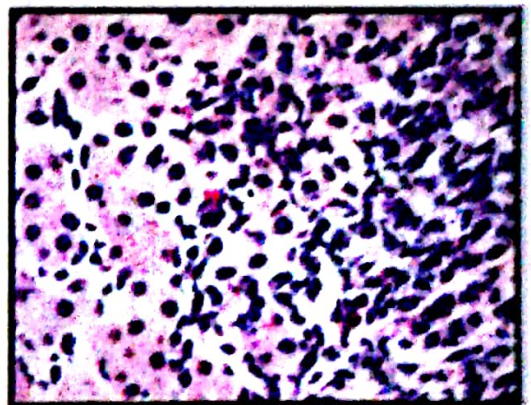


Fig.5.10: Autoimmune hepatitis, Lymphoplasmacytic infiltrate

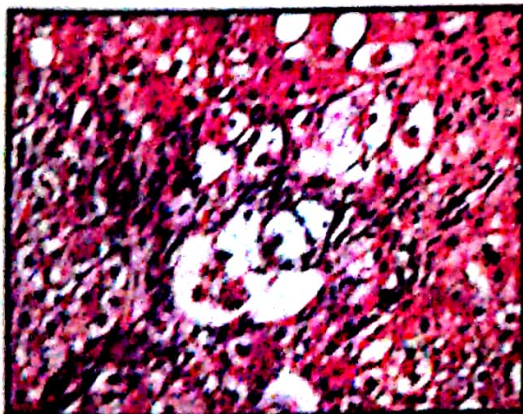


Fig.5.11: Alcoholic hepatitis, steatosis & inflammation

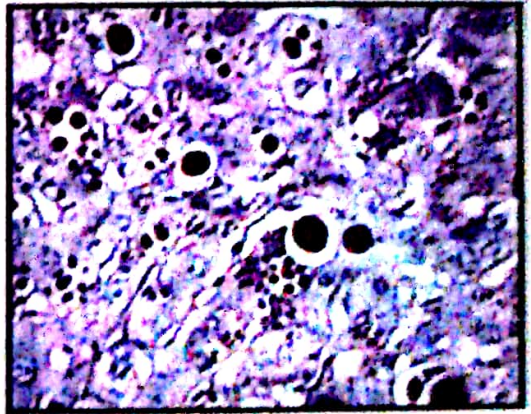


Fig.5.12: α -1-antitrypsin deficiency (PAS stain)

5. Alfa-1-anti-trypsin deficiency:

- Alfa-1-anti-trypsin is a serum protein synthesized in the liver and is immediately secreted in blood, where it has antiproteolytic properties.
- In this disorder, there are unusual phenotypes of α_1 -anti-trypsin which are not released from the liver cells after synthesis, they accumulate in the cytoplasm of hepatocytes as hyaline intracytoplasmic globules causing chronic hepatitis and cirrhosis.
- There may be associated pulmonary emphysema.

Microscopic:

- PAS positive globules in the hepatocytes (Fig. 5.12).
- Cholestasis and hepatocyte necrosis in newborn.
- Cirrhosis in children and adults.

Clinical: 1. Newborns present with cholestasis.
2. Children, adolescents and adults present with chronic hepatitis, cirrhosis or emphysema.

Cirrhosis

Definition: It is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

Its main characteristics are:

- Fibrous septa
- Parenchymal regenerating nodules
- Disruption of the architecture of the entire liver

Pathogenesis:

- ❑ The major pathologic mechanisms that combine to create cirrhosis are: liver cell necrosis, regeneration and progressive fibrosis.
- ❑ The normal liver contains collagens types I, III, V and XI in liver capsule, portal tracts and around central veins. A delicate framework of type IV collagen lies in the space between sinusoidal endothelial cells and hepatocytes "the space of Disse".
- ❑ In cirrhosis, types I and III collagen and other components of the ECM are deposited in all portions of the lobule.
- ❑ The major source of excess collagen in cirrhosis are the fat-storing perisinusoidal stellate (Ito) cell, which lies in the space of Disse. They activate and transform into myofibroblasts with increased synthesis and secretion of ECM and collagen production which initiates the process of cirrhosis.

Chapter 5: Diseases of the liver

The stimuli for activation of Ito cells and production of collagen are:

- Cytokines (TNF and IL-1) and reactive oxygen species produced by injured hepatocytes, Kupffer cells and endothelial cells.
- Activated stellate cells also release cytokines and TGF- β causing collagen synthesis.

NB: During the course of chronic liver disease, fibrosis is a dynamic process involving the synthesis, deposition and reabsorption of ECM components, modulated by changes in the balance between metalloproteinases and their tissue inhibitors. Thus, even in the late disease, if the disease process is halted or eliminated, significant remodeling and even restoration of liver function (*cirrhotic regression*) is possible.

Classification of cirrhosis:

I. Morphological classification:

Depending on the size of the parenchymal nodules.

1. **Micronodular cirrhosis:** The nodules range in size from less than 3 mm to 1 cm in diameter (*Fig. 5.13*).
2. **Macronodular cirrhosis:** This type is classically associated with chronic viral hepatitis or it is occasionally a result of submassive hepatic necrosis (*post-hepatitic or post-necrotic cirrhosis*).
The nodules are more than 1 cm in diameter (*Fig. 5.14*).
3. **Mixed cirrhosis:** Shows features of both types.

Any of the 3 previous types of cirrhosis may be: "**Active**" showing piecemeal necrosis, lobular activity and active fibrous septa formation or "**Inactive**" in absence of these previous data.

II. Aetiological classification:

1. **Viral hepatitis:** due to hepatitis B (with or without delta virus) and hepatitis C virus.
2. **Alcohol:** micronodular alcoholic cirrhosis.
3. **Cholestasis:** which leads to:
 - Primary biliary cirrhosis.
 - Secondary biliary cirrhosis.
4. **Autoimmune hepatitis:** It usually results in macronodular cirrhosis.
5. **Drugs and toxins.**
6. **Metabolic.**
 - Haemochromatosis; "pigment cirrhosis"
 - Wilson's disease
 - Alpha-1 antitrypsin deficiency.

Chapter 5: Diseases of the liver

- Type IV glycogen storage disease.
- Galactosaemia.
- Tyrosinaemia.

7. Cryptogenic.

Pathological features of different types of cirrhosis:

I. Posthepatic cirrhosis: The most common cause is previous viral infection (HBV - HCV).

Gross: The liver may be of normal size or shrunken.

Both outer and cut surfaces show irregular nodules of varying size.

Microscopic:

- The liver tissue shows loss of the normal lobular architecture.
- It is replaced by variable sized cirrhotic nodules separated by active or inactive fibrous tissue septa.
- The liver parenchyma shows varying degrees of liver cell degeneration and necrosis.
- The regenerating nodules may have residual or newly grown vascular structures but the normal relationship is not seen.
- Evidence of viral B or C aetiology may be detected.

II. Alcoholic cirrhosis:

- It occurs due to excessive or prolonged alcohol intake.
- Ethanol after absorption from the small intestine circulates to the liver where it is oxidized and catabolized to acetaldehyde. The latter is toxic to hepatocytes and may cause cell membrane damage and cell necrosis.

Gross: Micronodular cirrhosis.

The liver is firm yellowish and greasy to touch.

Microscopic: Cirrhotic liver with fatty change and Mallory bodies.

III. Primary biliary cirrhosis:

- It is a chronic liver disease in which there is progressive destruction of small intrahepatic bile ducts.
- It is considered to be an "autoimmune disease".
- The disease is more common in females.
- There is an increased titre of antimitochondrial antibody "AMA".

Gross:

- The liver is enlarged, deep-green in colour and shows micronodular cirrhosis.

IV. Secondary biliary cirrhosis:

It occurs due to extrahepatic biliary obstruction (Fig. 5.15):

1. Stone in the common bile duct.
2. Stricture of the common bile duct.
3. Tumours as carcinoma of the head of pancreas.

Gross: as in primary biliary cirrhosis

V. Haemochromatosis:

Liver cirrhosis occurs in both;

- a. Hereditary hemochromatosis
- b. Secondary haemochromatosis

Gross: The liver is enlarged, reddish brown in colour and it shows "micronodular cirrhosis".

Microscopic: Micronodular cirrhosis, with deposited iron pigments (Fig. 5.16).

Effects of cirrhosis:

1. **Portal hypertension:** It is an increase in the pressure in the portal circulation more than 5 - 10 mmHg. It is usually due to:
 - Pressure of regenerating nodules on the branches of the portal veins.
 - Development of anastomosis between the branches of the hepatic artery and portal vein with transformation of the higher arterial pressure to the portal veins.
 - Increase in portal venous blood flow due to hyperdynamic circulation. This is caused by arterial vasodilatation of splanchnic circulation resulting from increased production of nitric oxide in the vascular bed.

Portal hypertension leads to the following effects: —

- **Chronic venous congestion** in the portal draining area resulting in some disturbance in the function of the gastrointestinal tract.
- **Splenomegaly** which may induce hematological abnormalities.
- **Ascites** which is partly due to portal hypertension and partly due to the accompanying hypoproteinaemia.
- **Varicosities** in the anastomotic veins between the portal and systemic circulation which are:

At the lower end of the oesophagus (**oesophageal varices**), rupture may lead to severe and fatal haematemesis.

At the lower end of the rectum (**piles or haemorrhoids**).

Around the umbilicus (**caput medusa**).

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2. Hypoproteinaemia due to decreased synthesis of albumin with decrease in the osmotic pressure of the plasma proteins leading to oedema and ascites.
3. Failure of the normal inactivation of estrogen by the liver leading to atrophy of the testis and hyperplasia of the breast in the male i.e. gynaecomastia.
4. Hepatocellular carcinoma is a complication of cirrhosis of viral aetiology (HBV & HCV), α -1-antitrypsin deficiency, primary haemochromatosis and alcoholism.
5. Liver cell failure: Cholemia is the usual end result.



Fig. 5.13 : Micronodular cirrhosis.

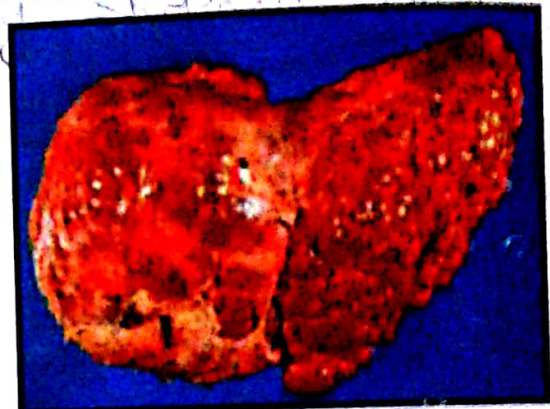


Fig. 5.14 : Macronodular cirrhosis.

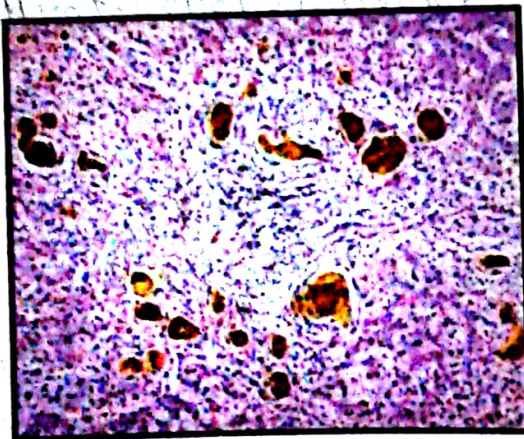


Fig. 5.15: Extrahepatic biliary tract obstruction.

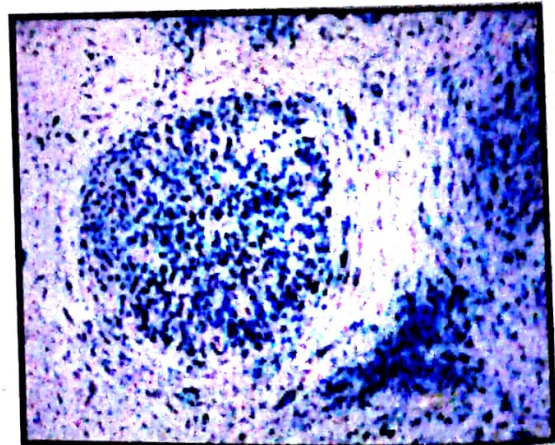


Fig. 5.16: Hereditary hemochromatosis (Perl's stain).

Other inflammatory and infectious diseases-

Amoebic liver abscess:

- It is an important complication of amoebic dysentery.
- Amoeba is carried to the liver by the portal circulation, where it releases enzymes causing liquefactive necrosis.
- In over 50% of cases a solitary abscess is found, but in other cases multiple abscesses of varying sizes are seen.

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Gross:

- ♦ The abscess is commonly in the right lobe.
- ♦ The wall of an acute abscess is irregular, greyish brown in colour with streaks of blood ("café au lait" or resembling Anchovy sauce).
- ♦ Chronic abscess has a regular smooth outline.

Microscopic:

- ♦ It is composed of liver cells showing liquifactive necrosis surrounded by mononuclear cells together with granulation tissue and little fibrosis.
- ♦ Occasional amoebae may be visible in the necrotic tissue surrounded by a clear halo, it has spherical nucleus.

Complications of amoebic liver abscess:

These are mainly due to pressure or due to perforation in different sites:

1. The abscess may burst in the peritoneal cavity giving "peritonitis".
2. It may become adherent to the transverse colon or stomach and burst through one of them.
3. Abscess near to the upper surface, presses on the lymphatics producing pleural effusion on the right side.
4. The abscess may become adherent to the diaphragm and then it ruptures into the right pleural cavity or into the pericardium.
5. The amoebae may gain access to the systemic circulation forming amoebic abscesses in the lung, spleen and very rarely in the brain.

Pyogenic liver abscess:

Suppurations of the liver occur through one of the following ways:

1. Hepatic artery: in systemic pyaemia.
2. Portal vein:
 - Portal pyaemia.
 - Actinomycosis, usually secondary actinomycosis of the caecum.
3. Infected amoebic abscess or hydatid cyst.
4. Direct spread of infection from nearby source.
5. Penetrating injury.
6. Ascending infection in the biliary tract (ascending suppurative cholangitis).

NB:

- Ascending suppurative cholangitis occurs as a complication, of acute suppurative cholecystitis or obstruction to the biliary passages by stones with superadded infection.
- In this case the liver is jaundiced and multiple small areas of suppuration are seen which represent dilated bile ducts filled with purulent material.

Tumours of the liver

The most common hepatic neoplasms are metastatic carcinomas. Primary hepatic malignancies, all almost are hepatocellular carcinoma.

Classification of tumors of the liver:

Epithelial tumors

- Benign:
 - Hepatocellular adenoma.
 - Intrahepatic bile duct adenoma.
 - Intrahepatic bile duct cystadenoma.
- Malignant:
 - Hepatocellular carcinoma.
 - Intrahepatic cholangiocarcinoma.
 - Hepatoblastoma.

Mesenchymal tumors

- Benign: Hemangioma →
- Malignant: Angiosarcoma →

Secondary tumors

A- Benign tumours:

(1) Liver cell adenoma: ←

It occurs **almost always** in women in the reproductive period especially those who take **contraceptive pills** for prolonged time.

Gross: This tumour is a well demarcated nodule that may be **pale, yellow-tan** or **bile-stained** (Fig. 5.17).

Microscopic: It is composed of benign looking hepatocytes not arranged in a lobular architecture. The portal tracts or the central venules are **not present**.

(2) Bile duct adenoma: →

- It is more common in males.
- It is usually less than 1 cm in diameter and it is **white in colour**.

Microscopic: It is composed of branching bile duct-like structures in a dense fibrous stroma.

(3) Cavernous haemangoma: →

- It is the most common benign tumour of the liver.
- It occurs at all ages and in both sexes.

Gross: It is usually small, less than 5 cm in diameter.

Chapter 5: Diseases of the liver

Microscopic: It is composed of large non-communicating vascular spaces lined by flat endothelium.

Clinical: - Small tumours are asymptomatic

- Larger tumours (may reach 30 cm) can cause:

- o Severe pain
- o Abdominal swelling
- o Haemo-peritoneum

B-Primary malignant tumours of the liver:

1. Hepatocellular carcinoma "HCC":

- o It is the most common malignant tumour arising from the hepatocytes.
- o Peak age incidence is between 40-50 years.
- o It is more common in males than females with a ratio of 5:1.
- o The serum α -fetoprotein (AFP) is elevated in 80% of cases.

Pathogenesis of hepatocellular carcinoma

1- The three major aetiological mechanisms are:

- Infection with viral hepatitis (HBV & HCV)
- Alcoholic cirrhosis
- Aflatoxin exposure

2- The tumorigenic capacity of HBV & HCV is probably through causing chronic inflammation and increased cell turnover.

3- Cirrhosis as alcoholic, α -1-antitrypsin deficiency and hemochromatosis.

4- Cellular dysplasia: most HCC develop from small cell, high grade dysplastic nodules in cirrhotic livers.

5- Aflatoxin: Derived from the fungus "Aspergillus flavus", found in moldy grains and peanuts. It can bind to cell DNA causing mutation in P53.

6- Other risk factors include: age, gender, chemicals and nutrition.

7- Acquired mutations in oncogene β -catenin or suppressor gene TP53.

Gross: The liver is usually enlarged, the tumour is soft, tan grey or green, (bile stained) often with foci of haemorrhages and necrosis.

HCC may grossly appear as:

- **Unifocal:** usually massive tumour (Fig. 3.18).
- **Multifocal:** tumour made of nodules of variable size
- **Diffuse infiltrative:** tumour may involve the entire liver.

Microscopic:

- ❑ **Well-differentiated HCC:** The neoplastic cells are arranged in cords, trabeculae or glandular patterns and may contain bile pigment.
- ❑ **High grade tumours** are composed of anaplastic giant cells.
- ❑ The stroma is scant in most cases of HCC.

- A distinctive variant of HCC is the fibrolamellar type that occurs in young adults, without cirrhosis or other risk factors.

2. Bile duct carcinoma "cholangiocarcinoma":

- It is a primary malignant tumour of the liver arising from the bile duct epithelium.
- It occurs in old age group; common above 60 years.
- The sex incidence is 1:1 in both males and females.

Risk factors: It is associated with primary sclerosing cholangitis, chronic disease of biliary tract and exposure to Thorotrast.

Gross: The tumour is firm to hard and whitish.

Microscopic: It is an adenocarcinoma with abundant fibrous tissue stroma.

3. Angiosarcoma:

It is a malignant vascular tumour arising from the endothelial cells lining the sinusoids.

Gross: Enlarged liver with multiple purplish haemorrhagic masses.

Microscopic:

- The tumor is composed of infiltrative, freely anastomosing vascular channels.
- The tumor cells grow along the sinusoids, they have anaplastic pleomorphic nuclei showing mitotic activity.

4. Hepatoblastoma:

It is the most common primary hepatic tumour in children.

Gross: Partially encapsulated solitary mass in the right lobe of the liver.

The cut surface shows areas of necrosis, haemorrhage and spotty calcification.

Microscopic: Mixture of epithelial (fetal or embryonal type hepatocytes) and mesenchymal elements.

II. Secondary "metastatic" hepatic tumours:

They are much more common than primary malignant tumours of the liver. They reach the liver by:

1. Direct infiltration: From carcinoma of nearby organs such as the stomach, gall bladder and colon.
2. Via blood: through:
 - Portal veins: from carcinoma of the colon and rectum and carcinoma of the head of the pancreas.

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- Hepatic artery, from carcinoma of the lung, carcinoma of the breast, renal cell carcinoma, malignant melanoma and osteosarcoma.

Gross:

- The liver is usually enlarged and is infiltrated by multiple nodules of variable size usually greyish-white in colour or dark brownish in cases of malignant melanoma or choriocarcinoma.
- The larger nodules show depressed necrotic centres and appear umbilicated (Fig 5.20).



Fig. 5.17: Liver cell adenoma

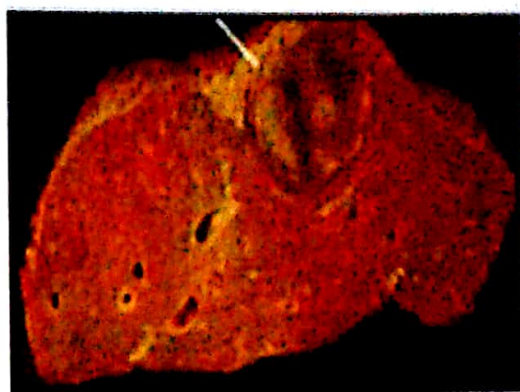


Fig. 5.18: Unifocal HCC

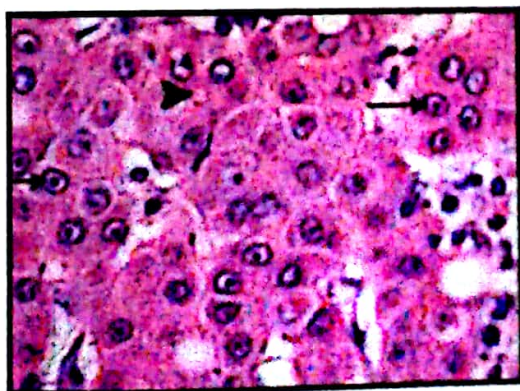


Fig. 5.19: Well differentiated HCC



Fig. 5.20: Liver, multiple metastatic nodules

Jaundice

It is yellowish discolouration of the skin, sclera, and mucous membrane due to increase of serum bilirubin more than 2-3 mg (Normal value 0.2 - 1.2 mg).

Metabolism of bilirubin (Fig. 5.22):

- Bilirubin is formed from the haem fraction of the haemoglobin after breakdown of the red blood cells in the spleen and bone marrow.
- The bilirubin thus formed is insoluble in water and is kept in solution in the plasma by its firm attachment to albumin.

- In the liver, bilirubin is detached from the albumin and becomes attached to a protein called "diglucuronide" resulting in a water soluble conjugated bilirubin, which is excreted in faeces as "stercobilinogen".
- Some of it is absorbed by the blood and is excreted in the urine as "urobilinogen"

Types of jaundice:

1. Haemolytic jaundice.
2. Hepatocellular jaundice.
3. Obstructive jaundice.

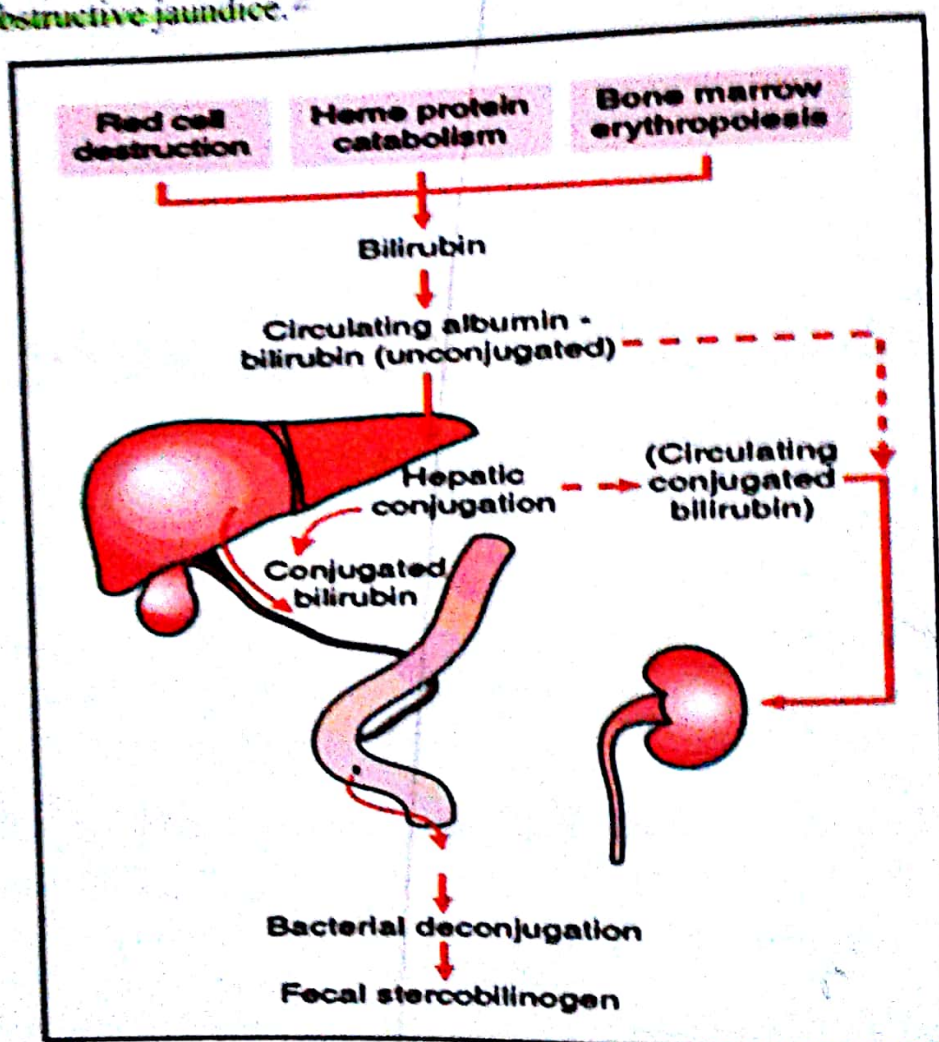


Fig.5.22: Bilirubin metabolism and elimination

Aetiology and pathogenesis of jaundice:

Predominantly unconjugated hyperbilirubenemia

1. Excessive production of bilirubin (haemolytic jaundice): As in haemolytic anaemia.
2. Reduced hepatic uptake of bilirubin: Drug (e.g. rifampicin) interferes with membrane carrier systems.

3. Impaired conjugation of bilirubin: Physiologic jaundice of the newborn
Predominantly conjugated hyperbilirubinaemia
4. Impaired excretion of conjugated bilirubin: Hepatocellular damage, e.g. viral hepatitis, toxins and drug induced hepatitis.
5. Intrahepatic cholestasis: Failure of biliary flow down the biliary tree and this occurs in; viral hepatitis, alcoholic hepatitis, certain drugs (e.g. chloropromazine, estrogen) and primary biliary cirrhosis.
6. Extrahepatic cholestasis (Extrahepatic obstructive Jaundice): occurs with; gall stones obstructing the common bile duct and carcinoma of the common bile duct and cancer head of pancreas.

Diseases of the Gall Bladder

Cholecystitis:

It is inflammation of the gall bladder, may be acute, chronic or acute superimposed on chronic.

Acute cholecystitis: Types;

1. Acute calculous cholecystitis: due to obstruction of gall bladder neck or cystic duct by gall stone.
The pathogenesis is thought to be chemical due to changes in the concentration and composition of bile or ischaemic rather than infectious.
2. Acute acalculous cholecystitis (no gall stones): it may follow major non-biliary surgery, severe trauma, severe burn or associated with septicaemia, typhoid fever or polyarteritis nodosa.

Gross:

- The gall bladder is usually enlarged and tense.
- The wall is remarkably thickened by oedema.
- The peritoneal covering is congested and covered by fibrinous or in severe cases fibrinopurulent exudate.
- The mucosa is congested red in colour.
- Gall stones are found within the lumen in 90% of cases.
- On rare occasions, when obstruction of the cystic duct is complete and bacteria have invaded the gall bladder the cavity may be distended by pus ("Empyema of the gall bladder" Fig. 5.23).
- In more severe cases the wall becomes necrotic green-black in color "Gangrenous cholecystitis".

Microscopic:

- The mucosa may be intact or shows focal or extensive ulceration.
- The wall shows: oedema, haemorrhage and neutrophilic infiltrate.
- In severe cases abscess formation or gangrenous necrosis occurs.

Chronic cholecystitis:

It is the most common disease of the gall bladder and it is usually associated with gall stones. It may result from repeated attacks of acute cholecystitis, or more often from long standing gall stones.

Gross:

- The gall bladder is normal in size or small and shrunken.
- The serosa may show fibrous adhesions to the surrounding structures.
- The wall of gall bladder is thickened by fibrosis.
- The mucosa may be focally ulcerated and atrophic or intact.
- Gall stones are usually found within the lumen.

Microscopic:

- The mucosa may be relatively normal, atrophic or shows hyperplastic, metaplastic changes, and varying degrees of mononuclear cell infiltration.
- The gall bladder wall shows fibrosis.
- Invagination of the mucosa within the wall is known as "**Rokitansky Aschoff sinuses**" which represent diverticulae.

N.B.:

- **Hydrops of the gall bladder;** is distended gall bladder filled with clear watery fluid due to obstruction of the cystic duct or the neck of gall bladder.
- **Mucocele of the gall bladder;** is associated with more chronic obstruction in which the gall bladder is distended with mucinous material (Fig.5.24).

Cholesterosis of the gall bladder:

It is the accumulation of cholesterol-laden macrophages within lamina propria of the gall bladder (Fig.5.25).

Gross: The mucosa shows linear yellowish streaks surrounded by congested areas, "strawberry gall bladder".

Cholelithiasis:

It is defined as the presence of stones within the lumen of the gall bladder or in the extrahepatic biliary tree.

Gall stones are classified according to the chemical nature into (Table 5.2):

I. Cholesterol stones (Fig. 5.26):

- They are more common in females than males especially in users of oral contraceptive and in women with several pregnancies.
- Normally, cholesterol is held in solution by the action of bile salts.
- Pathologically, gall stones are formed in the presence of bile containing an excess of cholesterol or decreased bile salts. Such bile is supersaturated with cholesterol and is termed "lithogenic".

Cholesterol stones may be:

1- Pure cholesterol stones: Which contain 90% or more cholesterol.

- They account for 10% of all gall stones.
- They are typically single measuring from 1 mm up to 4 cm, round or oval in shape with mulberry-like surface.
- They are white or yellowish in colour and the cut surface is crystalline.

2- Mixed gall stones: They are the most common type in 80 % of cases.

- They consist of various combination of cholesterol, calcium bilirubinate and calcium carbonate.
- They are multiple faceted yellowish in colour and the size ranges from 1-2 cm.
- These stones are usually associated with "chronic cholecystitis".

II. Pigment stones:

- They result from precipitation of bilirubin as calcium bilirubinate.
- Pigment stones are divided into 2 different types namely:

1. Black stones:

- They are the most common stones associated with chronic haemolytic condition and liver cirrhosis.
- The increase in the unconjugated bilirubin is the most important factor in their pathogenesis.
- 50% of these stones are radio-opaque.
- Black stones appear black or deep brown with irregular shiny surface. The cut surface has glassy appearance.

2. Brown stones: They are radiolucent.

- They are much softer than black stones and they have dull brown appearance.
- The cut surface is laminated. These stones are associated with biliary stasis and chronic cholecystitis.

The gall bladder in cholelithiasis appears either normal especially with cholesterol and black stones or may show the picture of chronic cholecystitis in the cases of mixed or brown stones.

Table 5.2: Pathological features of different types of gall stones

Pathological Features	Cholesterol stone		Pigment stone	
	Pure	Mixed	Black	Brown
1 - Incidence	10% of all gall stones	80% of all gall stones	10% of all gall stones	
2 - Number	Solitary	Multiple	Multiple	Multiple
- Colour	White or pale yellow	Yellowish brown	Shiny black	Dull brown
- Size	1mm - 4 cm	1 - 2 cm.	Few mms	Few mms
- Shape and outer surface	Rounded or oval and mammilated	Faceted, smooth	Irregular friable	Irregular, more friable
- Cut surface	Crytalline.	Laminated	Glassy	Laminated
- Constituents	90% cholesterol	Cholesterol + Calcium Bilirubinate + Calcium Carbonates + Protein.	Calcium Bilirubinate + Calcium Carbonate	mainly Calcium Bilirubinate + Calcium strearate
- Radiodensity	Radiolucent	Radio opaque	50 % radio opaque	Radiolucent
- Gall bladder pathology.	Cholesterolosis	Cholecystitis	Unremarkable	Cholecystitis.

Complications of gall stones:

1. Biliary colic:
2. Infection as acute or chronic cholecystitis.
3. Obstruction:
 - In the biliay tree: leading to obstructive jaundice or pancreatitis.
 - In cystic duct: leading to empyema or hydrops of the gall bladder.
 - In the lower end of ileum after fistula formation between the gall bladder and intestine forming a cholecystenteric fistula and may lead to acute intestinal obstruction.
4. Perforation: occurs in severe cases, leading to acute suppurative peritonitis.

5. Squamous metaplasia of the columnar epithelium.
6. Malignant transformation into carcinoma of the gall bladder.

Tumours of the gall bladder

I. Benign tumours:

1. Adenoma: which may be sessile or pedunculated and exhibits tubular, tubulo-villous or villous pattern.
2. Adenomyoma: due to combination of smooth muscle proliferation and reactive mucosal changes of chronic cholecystitis and cholelithiasis.
3. Fibroma, lipoma, leiomyoma have also been recorded.

II. Malignant tumours:

Carcinoma of the gall bladder:

- It is more frequent in females than males, frequent at 7th decade.
- It is usually associated with gall stones.

Gross:

- The common site is the fundus of the gall bladder.
- It is mostly infiltrative with thickening of the wall.
- Occasionally it is exophytic and grows into the lumen of the gall bladder as irregular cauliflower-like mass. (Fig. 5.28).

Microscopic:

- It is an adenocarcinoma, may be papillary or poorly differentiated.
- Squamous cell carcinoma on the top of squamous metaplasia.

Spread:

1. Lymphatic spread: to the portal hepatic lymph nodes.
2. Direct spread to the liver and bile ducts.
3. Blood spread:



Fig. 5.24: Empyema of gall bladder



Fig. 5.25: Mucocoele of gall bladder

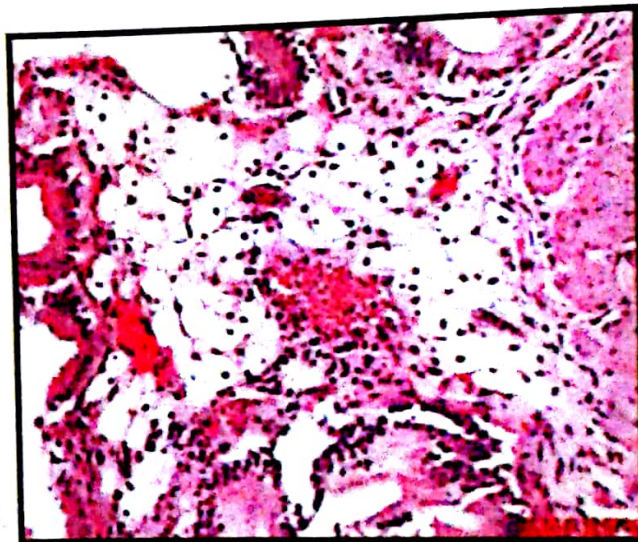


Fig. 5.26: Cholesterolosis



Fig. 5.27: Gall stones; yellow cholesterol & green pigmented stones



Fig. 5.28: Carcinoma of gall bladder

SUMMARY

Viral hepatitis

1. **Hepatitis A:** RNA virus and transmission through fecal-oral route. No chronic condition. No carrier & infection leads to long life immunity.
2. **Hepatitis B:** DNA virus. Transmission; parenteral, body fluids or through sexual contact. Leads to chronic carrier, fulminant hepatitis, chronic hepatitis, cirrhosis & hepatocellular carcinoma
3. **Hepatitis C:** Parenterally transmitted disease. Leads to chronic liver disease, cirrhosis & hepatocellular carcinoma.

Microscopic: Ballooning degeneration, cholestasis, lytic necrosis, apoptosis, bridging necrosis, liver cell regeneration, hyperplasia of kupffer cells & portal mononuclear inflammation. submassive or massive hepatic necrosis.

Chronic hepatitis; In 10% of B & in 40 - 60% of HCV.

Microscopic: Portal inflammation; piecemeal necrosis, necrosis & fibrosis

Other causes of chronic hepatitis are: Autoimmune, alcoholic, drug-induced hepatitis, Wilson disease & Alfa-1-anti-trypsin deficiency;

Cirrhosis; It is a diffuse process characterized by fibrosis and loss of normal liver architecture. *liver cell necrosis, regeneration and progressive fibrosis.*

Causes; Viral hepatitis, alcohol, cholestasis & metabolic diseases.

Effects of cirrhosis: Portal hypertension, hypoproteinaemia, failure of the normal inactivation of estrogen by the liver, HCC & liver cell failure

Liver abscesses: Amebic & suppurative.

Tumours of the liver: Liver cell adenoma & haemangioma.

Hepatocellular carcinoma "HCC":

Pathogenesis; viral hepatitis (HBV & HCV), cirrhosis, dysplasia; aflatoxin.

Gross: HCC may appear as unifocal, multifocal or diffuse infiltrative tumor.

Microscopic: Well- poorly differentiated adenocarcinoma, fibrolamellar type.

Bile duct carcinoma; adenocarcinoma with abundant fibrous stroma.

Secondary "metastatic" hepatic tumour: usually multiple nodules

Jaundice; definition, types & aetiology

Diseases of Gall bladder:

Cholecystitis: Acute cholecystitis (calculous, acalculous & gangrenous), empyema of the gall bladder.

Chronic cholecystitis: *Hydrops & mucocele of the gall bladder.*

Cholelithiasis: Cholesterol (Pure & mixed stones), pigment stones.

Tumours of the gall bladder: Adenoma, adenomyoma & carcinoma.

Chapter 6

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- ❏ Define pancreatitis, list types, and explain pathogenesis and morphological features.
- ❏ Compare and contrast between acute and chronic pancreatitis.
- ❏ Define diabetes mellitus, list types and explain pathogenesis.
- ❏ Describe the pathologic features and complications of diabetes mellitus.
- ❏ Compare and contrast between type 1 & 2 diabetes mellitus.
- ❏ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.
- ❏ Classify pancreatic duct carcinoma, explain pathogenesis and describe pathological features.
- ❏ Define endocrine tumours of the pancreas and describe pathological features.
- ❏ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.

DISEASES OF THE PANCREAS

Congenital anomalies of the pancreas:

- Agenesis: Usually associated with widespread severe malformations that is incompatible with life.
- Hypoplasia: Both endocrine and exocrine elements may be involved.
- Annular pancreas: The pancreatic head encircles the duodenum and may cause obstruction.
- Pancreas divisum: Failure of two ducts to fuse.
- Aberrant (ectopic) pancreas: A rare anomaly, mostly in the stomach, duodenum, jejunum, Meckel's diverticulum and ileum.
- Duct anomalies: Duct of Wirsung may drain into common bile duct or an orifice high in the duodenum.

Diseases of exocrine pancreas:

I- Pancreatitis:

It is inflammation of the pancreas may be acute or chronic.

a- Acute pancreatitis:

~~Inflammation of the pancreas, which is almost always associated with acinar cell injury.~~

Etiological Factors:

1. **Metabolic:** ~~Alcohol, hyperlipoproteinemia, hypercalcemia, drugs (e.g. thiazides), genetic (mutation in trypsinogen and trypsin inhibitor genes).~~
2. **Mechanical:** ~~Gallstones, traumatic, perioperative injury.~~
3. **Vascular:** ~~Shock, atheroembolism, polyarteritis nodosa.~~
4. **Infection:** ~~Mumps, coxsackie virus.~~
5. **Idiopathic:** 10-20% of patients.

Pathogenesis (Fig.6.1):

The histological changes in acute pancreatitis are attributed to the liberation and inappropriate activation of pancreatic enzymes mainly **trypsin, lipase and elastase** (which are normally present in inactive form inside the acinar cells).

Mechanism of pancreatic enzyme activation:

- a. Pancreatic duct **obstruction.**
- b. Primary acinar **cell injury,**
- c. **Defective intracellular transport of proenzymes within acinar cells.**

- Role of trypsin:
 - Activates other proenzymes (protease, phospholipase).
 - Activates Kinin system and Hageman factor (activates clotting and complement system).
- The activated enzymes result in the following alterations:
 - Microvascular leakage to cause edema.
 - Fat necrosis by lipolytic enzymes. Liberated fatty acids combine with calcium forming scattered areas of calcification.
 - Acute inflammatory reaction.
 - Proteolytic destruction of pancreatic substances
 - Destruction of blood vessels and interstitial hemorrhage.
- Amylase enzyme will pass to the general circulation, so there is increase in the level of amylase in the serum and urine and this is diagnostic for acute pancreatitis.

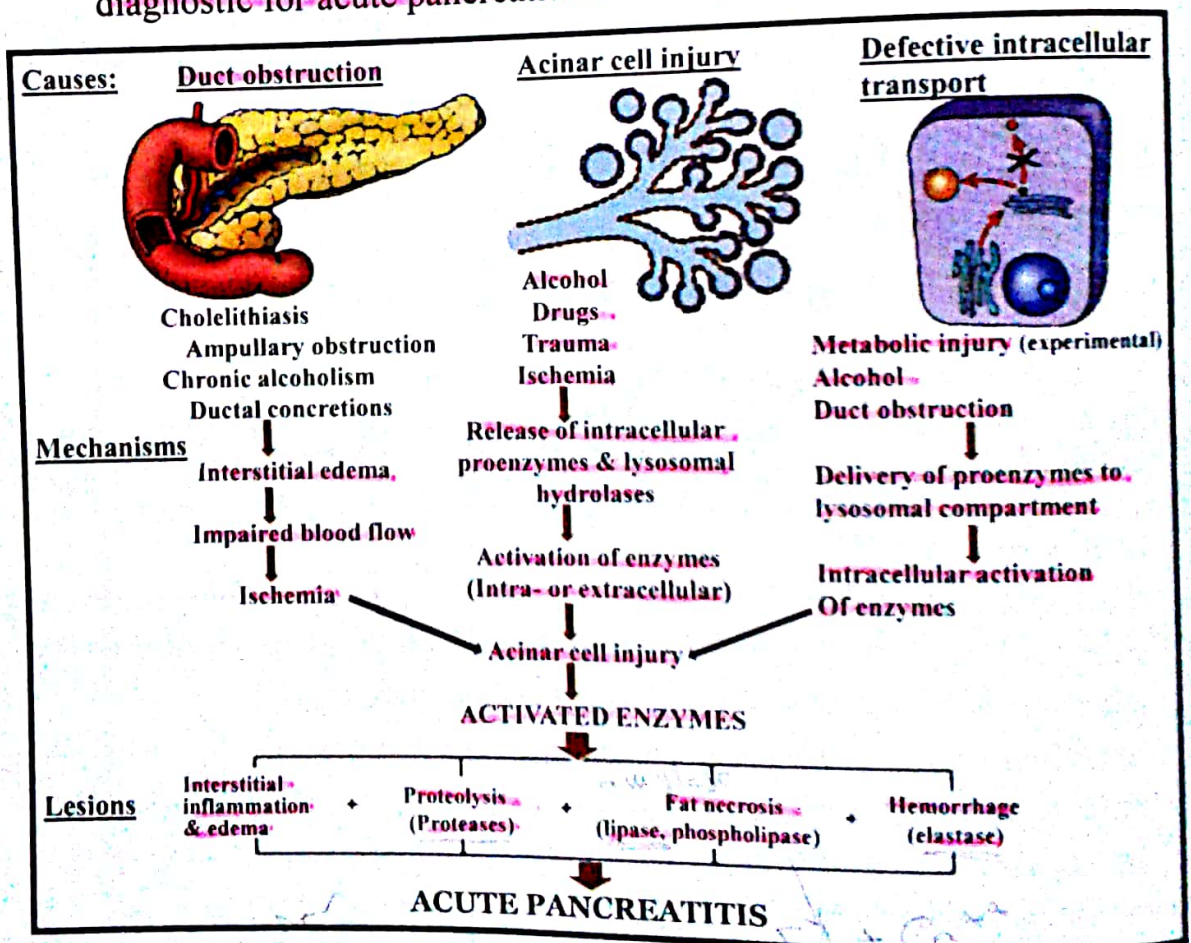


Fig.6.1: Pathogenesis of acute pancreatitis

Gross:

- In the early cases, the pancreas is enlarged, swollen and edematous.
- It shows some areas of blue-black hemorrhage and foci of yellowish-white chalky fat necrosis, seen in the pancreas as well as (Fig.6.2a) in the mesenteric and peritoneal fat.

Microscopic:

- Diffuse infiltration by acute inflammatory cells.
- Fat necrosis and extensive early dystrophic calcification.
- Hemorrhages and panlobular necrosis (Fig. 6.2b).
- The blood vessels are damaged leading to interstitial haemorrhages and may show thrombi.

Clinical features:

- Acute pancreatitis is a medical emergency.
- Abdominal pain is the cardinal manifestation: epigastric, radiating to the back, variable in severity.
- Shock: Due to pancreatic hemorrhage and release of vasodilating agents (Bradykinins and prostaglandins).
- Lab: Elevated serum amylase and lipase and hypocalcemia.
- Radiology: Enlarged inflamed pancreas.

Complications:

1. Disseminated intravascular coagulation.
2. Pancreatic abscess.
3. Pancreatic pseudocyst.
4. Death due to: shock, adult respiratory distress syndrome, acute renal failure.

Chronic pancreatitis

It is the progressive destruction of the pancreas with replacement by fibrous tissue due to repeated bouts of mild acute pancreatitis.

Etiology:

- Commonly affects middle-aged men, mostly alcoholics.
- However, it may be due to:
 - Pancreatic duct obstruction (e.g., by stones, divisum or neoplasms).
 - Familial hereditary pancreatitis.
 - Tropical pancreatitis (with genetic basis).
 - Cystic fibrosis, due to increased viscosity of secretions.

Pathogenesis:

1. Ductal obstruction by concretions: Protein hypersecretion from acinar cells as in alcoholics leads to precipitation of proteins forming ductal plugs.
2. Toxic metabolites: Toxins including alcohol can exert a direct toxic effect on acinar cells leading to lipid accumulation, acinar cell loss and fibrosis.
3. Oxidative stress: Alcohol-induced oxidative stress may generate free radicals in acinar cells leading to necrosis, inflammation and fibrosis.

Gross:

- The pancreas is hard in consistency due to fibrosis.
- It shows dilated ducts and calcified concretions.

Microscopic:

- Chronic inflammatory cell infiltrate around the ducts and lobules.
- Pancreatic ducts are dilated and show intra-luminal plugs.
- Ductal epithelium is either atrophied or hyperplastic or may show squamous metaplasia.
- The pancreatic tissue is replaced by excessive fibrosis with destruction of acinar tissue (Fig. 6.3) and later islets of Langerhans.
- Formation of pseudocysts.

Clinical picture: Repeated attacks of abdominal pain or may be silent.

Diagnosis:

- Clinical suspicion
- Laboratory and C.T finding of pancreatic calcifications.

Complications:

1. Loss of the acinar tissue leads to steatorrhea and malabsorption.
2. Loss of islands of Langerhans leads to secondary diabetes mellitus.

Diseases of Endocrine pancreas

Diabetes mellitus "D. M."

Diabetes mellitus represents a group of metabolic disorders in which there is impaired glucose utilization inducing hyperglycemia and glycosuria.

Types of diabetes mellitus:

I. Primary diabetes mellitus includes:

1. Type I diabetes mellitus: "Insulin - dependent diabetes mellitus "IDDM". It accounts for 10 - 20% of the cases.
2. Type II diabetes mellitus: "Non-insulin dependent diabetes mellitus" "NIDDM". It accounts for 80 - 90% of the cases.

II. Secondary diabetes mellitus due to:

- ☐ Chronic pancreatitis.
- ☐ Post-pancreatectomy.
- ☐ Hormonal tumors "Pheochromocytoma and pituitary tumors".
- ☐ Drugs "corticosteroids".
- ☐ Hemochromatosis.
- ☐ Genetic disorders "Lipodystrophy".

Type I diabetes mellitus: It is also called Juvenile-onset diabetes:

- ☐ It usually develops in childhood (<20 years), becoming manifested and severe at puberty. The patients depend on insulin for survival.
- ☐ This form of D.M. results from severe and absolute lack of insulin caused by a reduction in the beta cell mass.

Pathogenesis:

Islet cell destruction is due to:

1. Autoimmunity: There is evidence of implicating autoimmunity and immune-mediated injury as causes of beta cell destruction.
2. Genetic susceptibility: D.M. is HLA-D linked.
3. Environmental conditions: As viruses, chemical toxins, and cow's milk.

Type II diabetes mellitus: It is also called adult-onset diabetes.

It occurs in adults above 40 years.

Pathogenesis (Fig.6.5):

- ☐ Environmental factors as sedentary life style and dietary habits (obesity).
- ☐ Genetic factors (is more than in type I):
 - An inability of the peripheral tissue to respond to insulin "insulin resistance".
 - Beta cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia.

Pathological lesions:

The lesions in the pancreas are more likely to be prominent in type I than in type II D.M. One or more of the following lesions may present:

- ☐ Reduction in the size and number of islets (islet atrophy) especially in type I D.M.
- ☐ Leucocytic infiltration (lymphocytes and macrophages) of the islets which is called "insulinitis", it occurs in both types, but more severe in type I. Insulinitis occurs early and is often absent in clinically evident disease.
- ☐ Amyloid replacement of the islets especially in type II; in longstanding cases (Fig.6.4).

Complications of D.M.:

1. Ketosis and diabetic coma.
2. Ocular involvement: may take the form of retinopathy, cataract and glaucoma.

Chapter 6: Diseases of the pancreas

Retinopathy may be:

- Proliferative retinopathy: Retinal exudates, hemorrhage and microaneurysms.
- Non-proliferative retinopathy: Neovascularization and fibrosis.

These may lead to retinal detachments and blindness.

3. Nervous system complications: Diabetic patients are liable to cerebral hemorrhage and peripheral neuritis.
4. Cardiovascular complications:
 - o Atherosclerosis.
 - o Hypertension.
 - o Myocardial infarction.
 - o Gangrene of the limbs, is common either of moist or dry type due to ischemia.

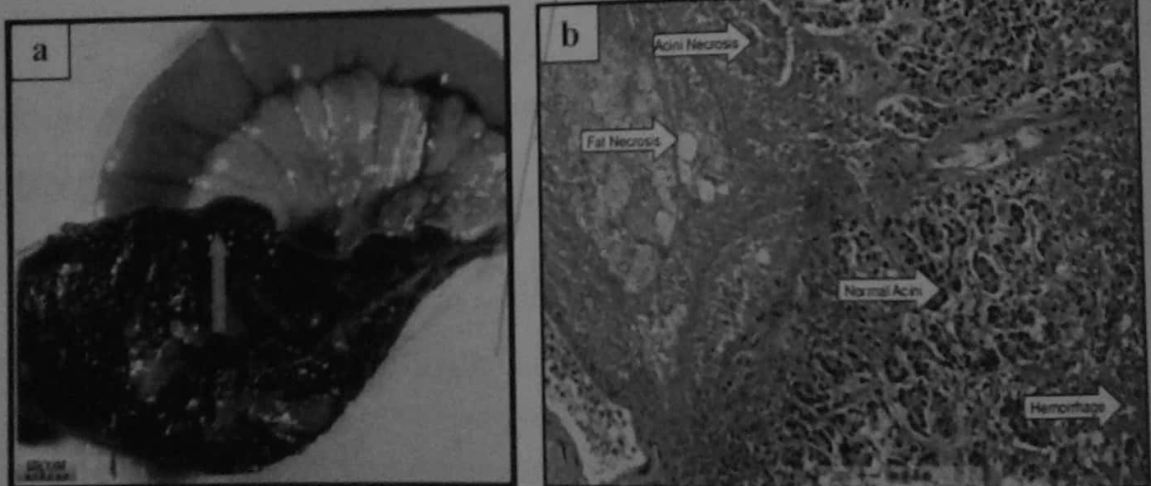


Fig.6.2: Acute hemorrhagic pancreatitis. (a) Gross (b) Microscopic

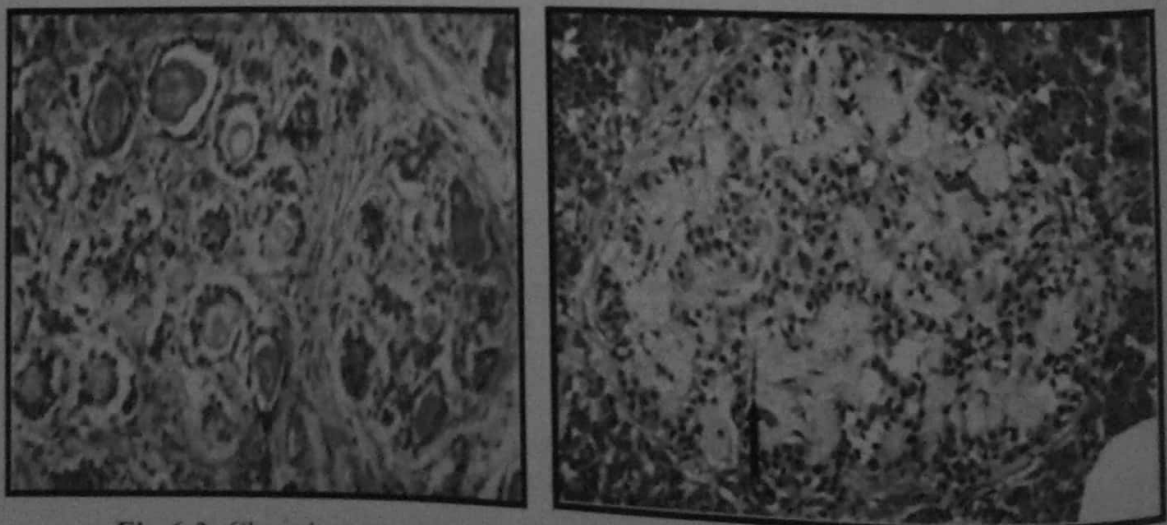


Fig.6.3: Chronic pancreatitis

Fig.6.4: Amyloid deposition of islet cells in type 2 DM

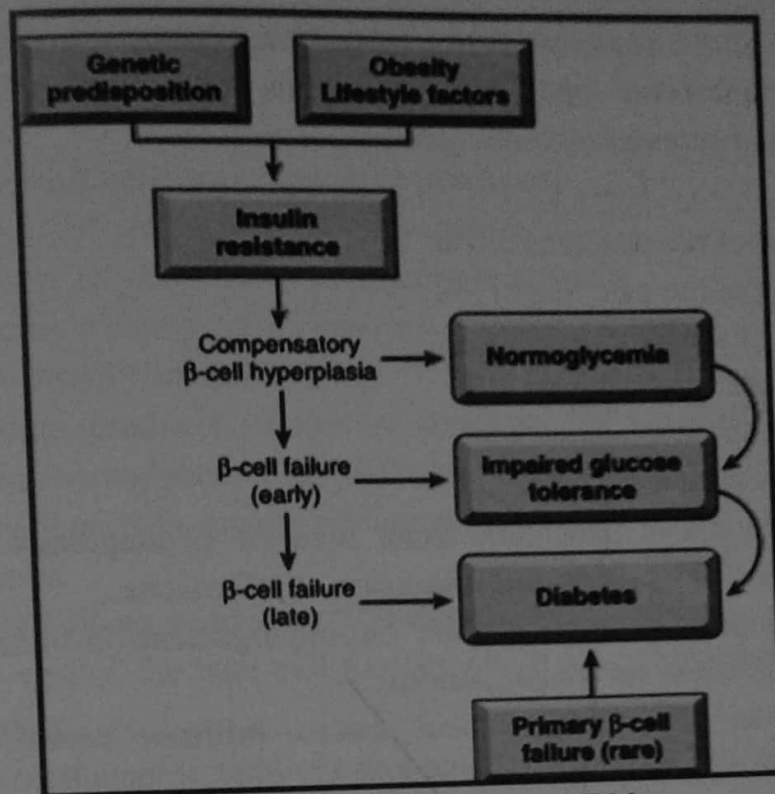


Fig.6.5: Pathogenesis of type2 DM

Tumours of the pancreas

I. Tumours of exocrine pancreas:

1. Cystic tumours include:

- a- Mucinous cystic tumour: They are multiloculated cystic neoplasms filled with mucinous secretions. They may be entirely:
 - 1) Benign: Mucinous cystadenoma.
 - 2) Malignant: Mucinous cystadenocarcinoma.
- b- Serous cystadenoma: It is a rare cystic tumour with serous secretion which is almost always benign.
- c- Solid-cystic "papillary cystic tumour": It is of low grade malignancy and seen predominantly in adolescent girls and younger women.

2. Carcinoma of the pancreas "Ductal adenocarcinoma":

- ☐ It is the fifth most frequent cause of death from cancer.
- ☐ Peak incidence 60-80 years.

Pathogenesis

- Predisposing factors include; diabetes mellitus, chronic pancreatitis and smoking. Familial clustering has been reported.

Chapter 6: Diseases of the pancreas

- Pancreatic cancer probably arises from precursor lesions (Pancreatic intraepithelial neoplasia), mutations of oncogenes (*K-RAS*) and tumor suppressor genes (*p53*).

Location:

1. Head of the pancreas: 60%
2. Body of the pancreas: 15%
3. Tail of the pancreas: 5%
4. Diffuse involvement: 20%

Gross: (Fig.6.6a)

- Gritty gray hard masses.
- Carcinoma of pancreatic head: Invasion of ampullary region with outflow obstruction and distension of biliary tree.
- Carcinoma of body and tail: No impingement on biliary tract and remain silent for longer periods.
- Extends into retroperitoneal spaces, infiltrate nerves, abdominal organs and lymph nodes.

Microscopic:

1. Adenocarcinoma: It is the most common histological type. The vast majority are moderate to poorly differentiated adenocarcinomas, made up of poorly formed glands in a densely fibrotic stroma (Fig.6.6b). Well-differentiated adenocarcinoma is rare.
2. Adenosquamous pattern.

Clinical picture:

- Usually silent until its extension impinges on other structures.
- Pain is usually the first symptom.
- The effect of carcinoma differs according to the site:
 - Tumors of the head of pancreas impinge on the ampulla of Vater, common bile duct and duodenum leading to obstructive jaundice and it may be discovered early.
 - Tumors of the body and tail grow silently to the adjacent structures and give early metastasis. They may be manifested by Trousseau's syndrome (migratory thrombophlebitis).
 - Tumor markers, e.g. CEA, CA 19-9 are elevated, but not specific enough to be useful for screening.

Diagnosis: CT scan and percutaneous biopsy are helpful.

II. Tumors of endocrine pancreas: "Islet cell tumors":

These tumors arise from islets of Langerhans's which contain different types of cells:

- ☐ Alpha or A cells which produce glucagon.
- ☐ Beta or "B" cells which produce insulin.
- ☐ Delta or "D" cells which produce somatostatin.
- ☐ "G" cells which produce gastrin.

1. Beta cell tumor "insulinoma".

This tumor produces excessive amounts of insulin which induce significant hypoglycemia associated with mental confusion and loss of consciousness. It is usually adenoma, less commonly it is carcinoma in 5% of cases.

2. Zollinger Ellison syndrome "Gastrinoma":

- It is one of the islet cell tumors which arise from the G cell of the pancreas.
- It is malignant in 60% of cases and benign in 40% of cases.
- It arises in the body and tail of pancreas, less commonly in the duodenum and antrum of the stomach.
- Patients with gastrinoma usually have "Zollinger Ellison syndrome" characterized by triad consisting of:
 - ☐ Peptic ulcerations in the stomach, duodenum and jejunum.
 - ☐ Gastric hypersecretion.
 - ☐ Islet cell tumor "Gastrinoma".

3. Alpha cell tumor "glucagonoma"

It is associated with increase serum levels of glucagon and a syndrome consisting of mild diabetes mellitus, necrotizing skin erythema and anemia.

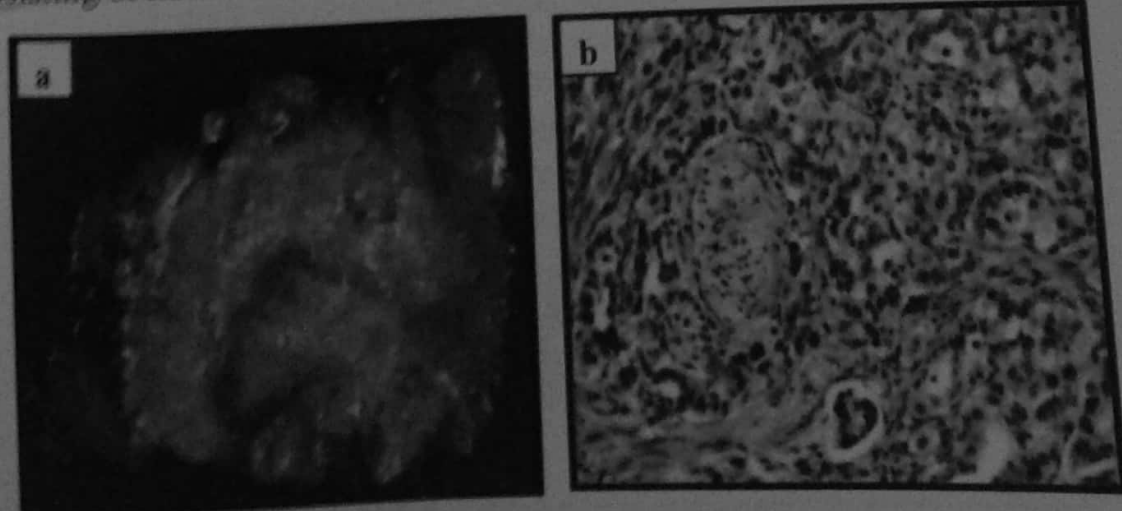


Fig.6.6: Pancreatic adenocarcinoma. (a) Gross (b) Microscopic

SUMMARY

Pancreatitis:

1- Acute pancreatitis: Inflammation with reversible parenchymal damage edema, fat necrosis parenchymal necrosis and hemorrhage;
Clinical manifestations vary from mild abdominal pain to a rapidly fatal vascular collapse.

2- Chronic pancreatitis is characterized by irreversible parenchymal damage and scar formation.

Causes; recurrent acute pancreatitis can result in chronic pancreatitis. Ductal obstruction and alcohol are the most common causes of both forms. Inappropriate activation of pancreatic digestive enzymes (due to mutations in genes encoding trypsinogen or trypsin inhibitors) and primary acinar injury (due to toxins, infections, ischemia, or trauma) also cause pancreatitis
Clinical manifestations: chronic malabsorption (due to pancreatic exocrine insufficiency) and diabetes mellitus (due to islet cell loss).

Pancreatic Neoplasms:

I. Pancreatic cancer probably arises from precursor lesions (PanINs), mutations of oncogenes (e.g., *K-RAS*) and tumor suppressor genes (*p53*).

Microscopic: Ductal adenocarcinomas with a dense stroma.

Clinical: Obstructive jaundice is a feature of the carcinoma of the head of the pancreas.

Diagnosis: CT scan and percutaneous biopsy.

II. Tumors of endocrine pancreas: "Islet cell tumors": *Types:*

- 1. Beta cell tumor "insulinoma"** produces insulin which induce hypoglycemia associated with mental confusion and loss of consciousness. It is usually adenoma, less commonly carcinoma (in 5%).
- 2. Zollinger Ellison syndrome "Gastrinoma":** It is malignant in 60% benign in 40% of cases, arises in the body & tail of pancreas, less commonly in the duodenum and antrum of the stomach.
- 3. *Clinical:*** Peptic ulcerations: in the stomach, duodenum and jejunum.
- 4. Alpha cell tumor "glucagonoma":** It is associated with increase serum levels of glucagon and a syndrome consisting of mild diabetes mellitus, necrotizing skin erythema and anemia.

Chapter 7

Intended Learning Outcomes ILOs:

By the end of this unit the students will be able to:

- ☐ Define Adult polycystic kidney disease, explain pathogenesis, describe its pathologic features and clinical course.
- ☐ Explain pathogenesis of glomerular diseases.
- ☐ Define nephrotic syndrome; list causes & describe pathologic features of each.
- ☐ Define primary glomerular diseases causing nephrotic syndrome, explain pathogenesis and describe light microscopic, IF and EM findings of each disease.
- ☐ Define nephritic syndrome; list causes & describe pathologic features of each.
- ☐ Describe the pathological features of diabetic glomerulosclerosis.
- ☐ Compare between nephrotic & nephritic syndrome.
- ☐ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.
- ☐ Describe the pathological features of acute & chronic pyelonephritis.
- ☐ Define drug-induced interstitial nephritis & compare between analgesic nephropathy & acute tubular necrosis.
- ☐ Compare benign & malignant nephrosclerosis.
- ☐ Define nephrocalcinosis; list types and complications.
- ☐ Define hydronephrosis; list causes and complications.
- ☐ Classify tumours of the kidney, recognize the predisposing factors and describe the pathological features of each.
- ☐ Recognize tumours of the renal pelvis and describe the pathological features.

DISEASES OF THE KIDNEY

Introduction to renal diseases:

- The kidney is a structurally complex organ that has evolved to carry out a number of important functions: excretion of the waste products of metabolism, regulation of body water and salt, maintenance of appropriate acid balance and secretion of a variety of hormones and autacoids.
- Diseases of the kidney are as complex as its structure, but their study is facilitated by dividing them into those that affect the four basic morphologic components: glomeruli, tubules, interstitium, and blood vessels.
- This traditional approach is useful because the early manifestations of diseases that affect each of these components tend to be distinctive. Furthermore, some components seem to be more vulnerable to specific forms of renal injury; for example, glomerular diseases are often immunologically mediated, whereas tubular and interstitial disorders are more likely to be caused by toxic or infectious agents.
- Nevertheless, some disorders affect more than one structure. In addition, the anatomic interdependence of structures in the kidney implies that damage to one structure almost always secondarily affects the others. Thus, severe glomerular damage impairs the flow through the peritubular vascular system; conversely, tubular destruction, by increasing intraglomerular pressure and inducing cytokines and chemokines, may induce glomerular sclerosis.
- Whatever the origin, there is a tendency for all forms of chronic renal disease ultimately to damage all four components of the kidney, resulting in chronic renal failure and what has been called *end-stage kidney disease*.
- The functional reserve of the kidney is large, and much damage may occur before functional impairment is evident.

Common presentations of renal diseases:

Patients with renal disease may present with one of the followings (Table 7.1):

Table 7.1: Common presentations of renal diseases

Acute renal failure ARF:	
• Rapid progressive decrease in renal function that is usually reversible. • Oliguria or anuria • Hypertension.	
Chronic kidney disease CKD:	
• Progressive decrease of glomerular filtration rate which is irreversible. • Symptoms of uremia. • Symptoms of anemia. • Symptoms of osteodystrophy.	
Acute nephritis (nephritic syndrome):	
• Oliguria • Hematuria	• Edema. • Hypertension.
(microscopic or macroscopic)	
Nephrotic Syndrome NS:	
• Proteinuria (more than 3.5 gm/24 hours). • Hypoalbuminemia.	• Edema. • Hyperlipidemia.
Asymptomatic urinary abnormalities:	
• Hematuria. • Proteinuria.	• Pyuria.
Renal tubule Defects:	
• Electrolyte imbalance. • Polyuria.	• Nocturia. • Symptoms of osteodystrophy.
Urinary tract infection (UTI):	
• Fever. • Dysuria and frequency of micturition	• Loin pain • Pyuria, bacteruria, leucocyte casts.
Stone Formation (nephrolithiasis):	
• Renal colic.	• Hematuria.
Urinary tract obstruction:	
• Oliguria up to anuria. • Renal colic.	• Hematuria. • Acute renal failure.
Hypertension:	

Congenital anomalies of the kidney and ureters

The most important congenital anomalies are:

1. **Renal agenesis:** The absence of both kidneys is not compatible with life. With agenesis (absence) of one kidney, the single kidney present enlarges sufficiently to maintain normal renal function (compensatory hypertrophy).

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2. **Hypoplasia:** Means congenitally small kidneys with a reduced number of nephrons but normal architecture.
3. **Horse-shoe kidney:** The two kidneys are united together, usually at their lower poles, by renal or fibrous tissue.
4. **Aberrant renal artery:** The renal artery enters the kidney at one pole, crossing the pelviureteric junction on its way. It may predispose to hydronephrosis and renal hypertension.
5. **Ectopic kidney:** Results from failure of ascent of one or both kidneys from the pelvis to the loin during embryonic development. The attached ureter may be "kinked", thus predisposing to hydronephrosis.
6. **Double ureter** with single or double renal pelvis.
7. **Congenital stricture of ureter.**
8. **Polycystic kidney disease:** *Presenting as a fetal lesion*
congenital polycystic
Megaureters associated
hydronephrosis

a- **Adult type polycystic disease (APKD):**

- ☐ **Autosomal dominant** polycystic kidney disease is characterized by multiple expanding cysts affecting both kidneys that destroy the intervening parenchyma. Cysts may arise at any level of the nephron from tubules to collecting ducts.
- ☐ Adult type polycystic disease may be associated with
 - Saccular aneurysms of the circle of Willis in 10% to 30%.
 - Asymptomatic liver cysts occur in one third of patients.

Pathogenesis:

- It is inherited as an autosomal dominant trait.
- In 85% to 90% of families, **PKD** is the defective gene.
- This gene encodes **polycystin-1** (a protein involved in cell-cell or cell-matrix adhesion).

Gross: Very large kidneys. The outer and cut surfaces show multiple cysts of various sizes up to 3-4cm with no intervening parenchyma. The cysts contain clear, turbid or hemorrhagic fluid (**Fig. 7.1**).

Microscopic: The cysts are lined by cubical to columnar epithelium.

Clinical: Flank pain, intermittent gross hematuria, hypertension, urinary tract infection and chronic renal failure in adult life

b- **Infantile type polycystic disease:**

- It is inherited as an autosomal recessive trait and kills shortly after birth.
- Enlarged kidneys with multiple cysts in the cortex and medulla.
- Liver may show multiple hepatic cysts and congenital hepatic fibrosis.

Complications:

HTN, CKD, hematuria



Fig. 7.1: Adult polycystic kidney.

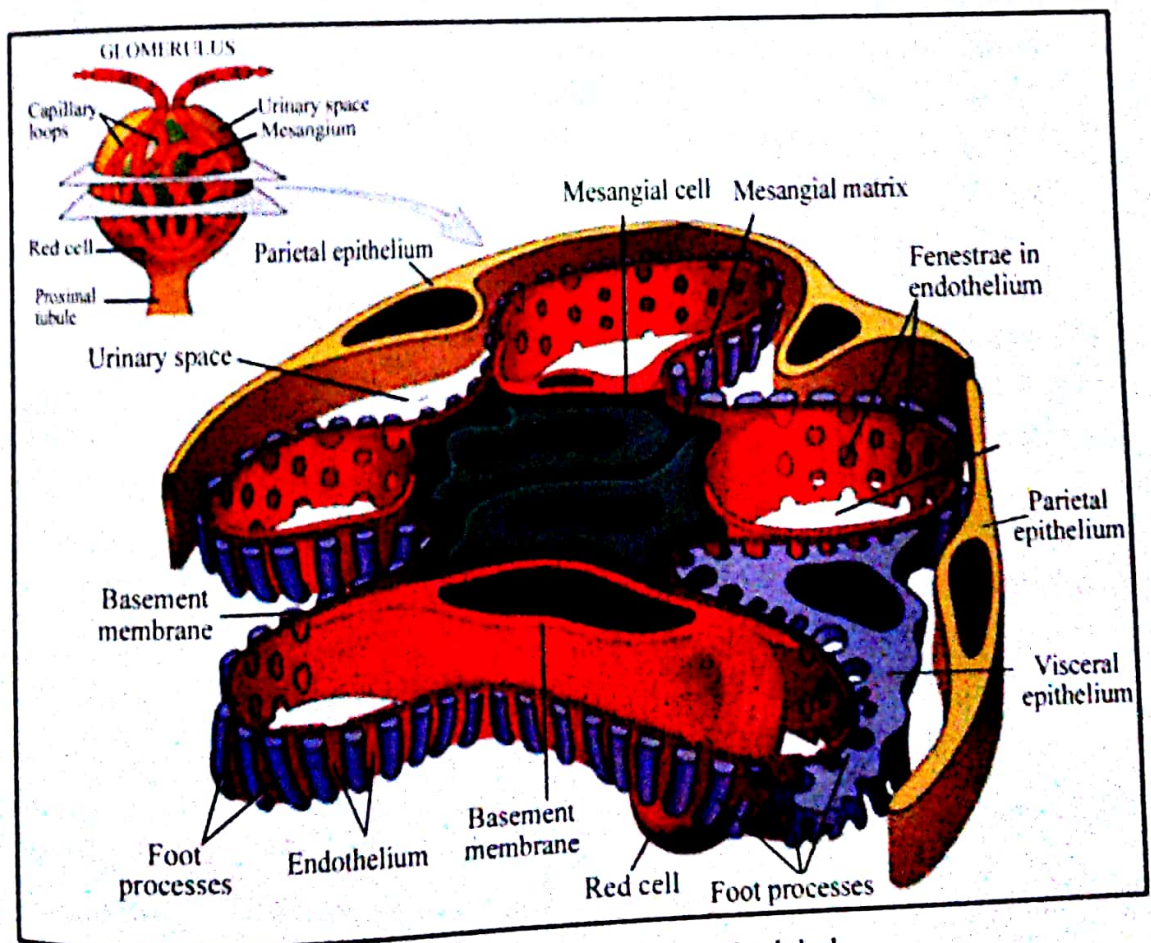


Fig. 7.2: Structure of the glomerular lobule.

Structure of the glomerulus (Fig. 7.2):

The glomerulus consists of an anastomosing network of capillaries invested by two layers of epithelium; the visceral epithelium (composed of podocytes) and the parietal epithelium which lines Bowman space (the cavity in which the plasma ultrafiltrate first collects).

The glomerular capillary wall is the filtration unit and consists of the following structures:

- A thin layer of fenestrated endothelial cells; *prevent macromolecules from crossing from blood in glomerular capillary into glomerular tuft*
- A glomerular basement membrane (GBM) with a thick, electron-dense central layer, the *lamina densa*, and a thinner, electron-lucent peripheral layers, the *lamina rara interna* and *lamina rara externa*. The GBM consists of collagen (mostly type IV), laminin, and several other glycoproteins.
- Podocytes; are cells with interdigitating processes embedded in and adherent to the *lamina rara externa* of the basement membrane.
 - ← Adjacent foot processes are separated by *filtration slits*.
- The glomerular tuft is supported by *mesangial cells* lying between the capillaries. Mesangial matrix forms a meshwork through which the mesangial cells are scattered.

← support
regulate matrix charge
← no charged protein in lumen

Glomerulonephritis (GN)

It is a disease characterized by structural or functional changes which occurs initially and primarily in the glomeruli. *immune-mediated*

Glomerulonephritis is either:

a- **Primary disease** involving only the kidneys.

b- A manifestation of **systemic disease**:

- Systemic lupus erythematosus (SLE)
- Infections e.g. viral B&C hepatitis, malaria, syphilis and Bilharziasis
- Neoplasia e.g. lymphoma.
- Diabetes mellitus
- Ingestion of drug (e.g. gold salts, penicillamine)

Pathogenesis of GN:

1. Glomerulonephritis caused by circulating immune complexes:

- The antigen is not of glomerular origin.
 - It may be *endogenous*, as in the GN associated with SLE.
 - Or *exogenous*, as is probable in the GN that follows certain bacterial (streptococcal), viral (hepatitis B), parasitic (*Plasmodium falciparum* malaria), and spirochetal (*Treponema pallidum*) infections. *non glomerular antigens Ag and Ab*
 - Often the inciting antigen is *unknown*, as in most cases of membranoproliferative GN (MPGN).
- Antigen-antibody complexes are formed in situ or in the circulation and are then trapped in the glomeruli.
- Immune complexes produce injury, in the large part, through the activation of complement and the recruitment of leukocytes.

2. Glomerulonephritis caused by in situ immune complexes

- Antibody deposition in the glomerulus is a major pathway of glomerular injury.
- Antibodies react directly with fixed or planted antigens in the glomerulus. *seen in SLE*
- Planted non-glomerular antigens as anti-nucleosomal complexes (in patients with SLE); bacterial products, such as endostreptosin, a protein expressed by group A streptococci.

NB: Immune complex deposition (circulating or in-situ) gives a **granular immunofluorescent pattern** (Fig. 7.3).

3. Anti-Glomerular Basement Membrane Antibody-Mediated GN:

- It results from the formation of autoantibodies directed against the GBM, E.g., Good pasture syndrome and anti-GBM antibody-mediated crescentic GN
- Deposition of these antibodies creates a **linear IF** staining pattern (Fig. 7.4).

NB: Immune complexes and antibodies cause injury by complement activation and leukocyte recruitment, with release of various mediators (Fig. 7.5) and sometimes by direct podocyte damage.

① localization of immune complex in glomeruli
lytic, attract, etc.
③ activation of alternative complement pathway

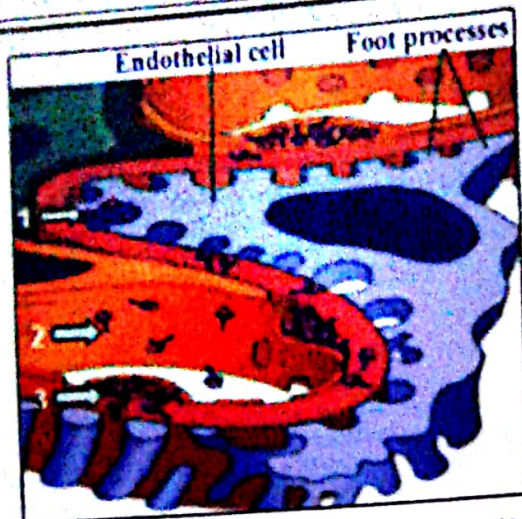


Fig. 7.3: Circulating immune complex (2) nephritis; granular IF deposits (1,3)

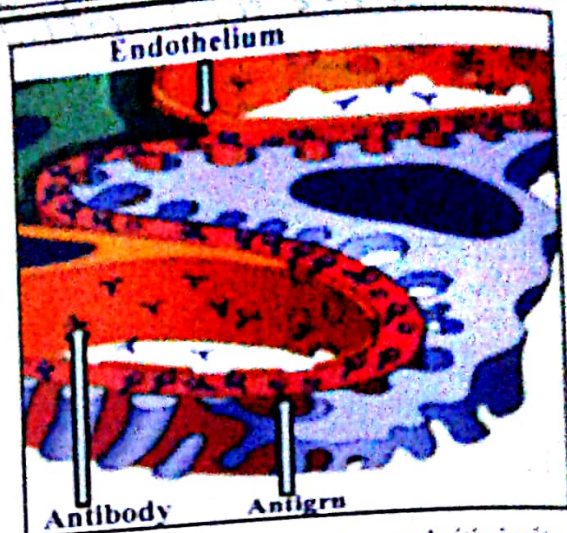


Fig. 7.4: Immune complex nephritis insitu Anti-GBM disease (linear IF deposits)

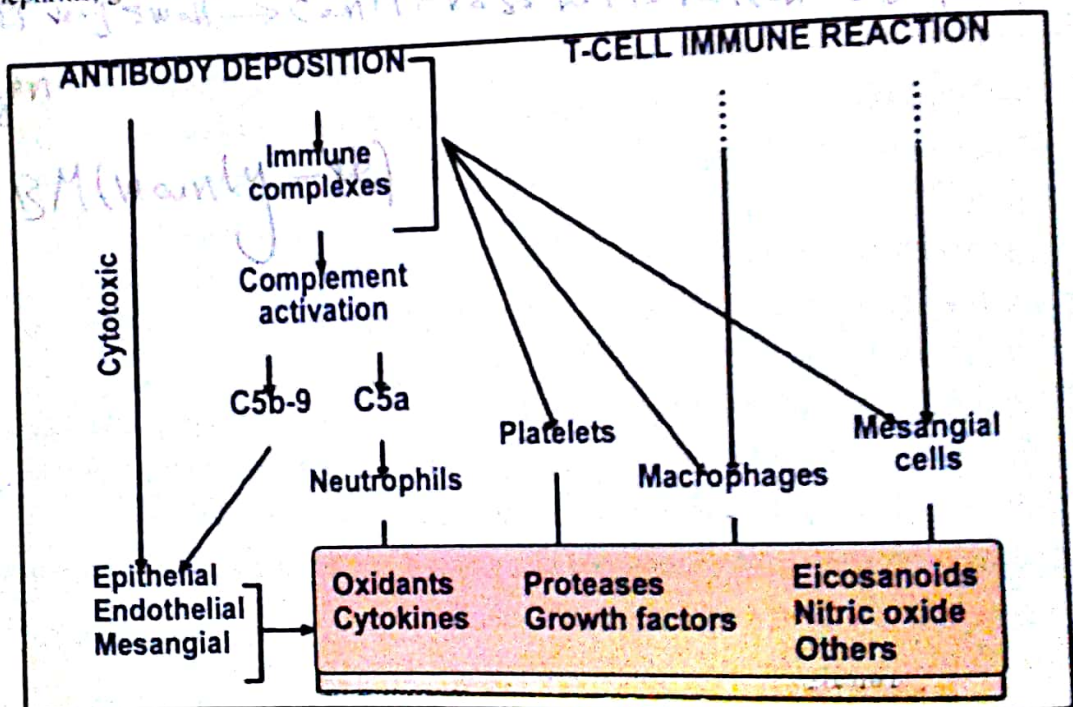


Fig. 7.5: Pathogenesis of glomerulonephritis

T cell immune reaction in; minimal change disease & focal segmental glomerulosclerosis

Microscopic features of immunologically mediated glomerular injury:

Regardless of the mechanism, the glomerular lesions usually consist of:

- leukocytic infiltration (exudation) into glomeruli.
- Hypercellularity due to proliferation of endothelial, mesangial and parietal epithelial cells.
- Electron microscopy reveals the immune complexes as electron-dense deposits or clumps: in the mesangium between the endothelial cells and

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the GBM (subendothelial deposits), or between the outer surface of the GBM and the podocytes (subepithelial deposits).

- The presence of immunoglobulins and complement in these deposits can be demonstrated by immunofluorescent microscopy
- Crescent formation is due to localized proliferation of the parietal epithelial cells of Bowman's capsule (capsular epithelium). This is probably initiated by escape of fibrin into the Bowman's space.
- Sclerosis due to collapsed glomerular capillary walls and capillary lumen obliteration.
- Sclerosis due to deposition of increased mesangial matrix in the mesangium and in areas of collapsed glomerular capillary walls.
- The above changes may be global (i.e. affecting the entire glomerulus) and diffuse (affecting all glomeruli) or segmental (affecting part or segment of the glomerulus) and focal (affecting only some glomeruli).

Nephrotic syndrome:

clinical-biochemical state. *Primary*
It refers to a clinical complex that induces: *Features* *Causes*

- Heavy proteinuria (daily loss in urine of 3.5gm or more).
- Hypoproteinaemia.
- Generalized oedema.
- Hyperlipidaemia and lipidauria. *post-tubular capillary*
↓
tubular

Causes of the nephrotic syndrome:

I. Primary renal diseases such as:

- ⊗ Membranous glomerulonephritis.
- ⊗ Minimal change glomerulonephritis → *Respond to steroids*
- ⊗ Focal segmental glomerulosclerosis.
- ⊗ Membranoproliferative glomerulonephritis

II. Secondary "systemic diseases" such as:

- ⊗ Diabetic glomerulosclerosis.
- ⊗ Renal amyloidosis.
- ⊗ Systemic lupus erythematosus (lupus nephritis).

lymphoma, drug, NSAIDs, syphilis, malaria, HIV

Pathogenesis of nephrotic syndrome:

- In nephrotic syndrome, the initial event is a derangement in the capillary walls of the glomeruli (fusion of foot processes), resulting in increased permeability to plasma proteins leading to **proteinuria**.
- With long-standing or extremely heavy proteinuria, serum albumin is decreased, resulting in **hypoalbuminemia**.
- The **generalized edema** of the nephrotic syndrome is, in turn, a consequence of the drop in plasma colloid osmotic pressure as a result of hypoalbuminemia.

As fluid escapes from the vascular tree into the tissues, there is a concomitant drop in plasma volume, with diminished glomerular filtration volume. This leads to increased release of renin which in turn stimulates the angiotensin-aldosterone axis promoting retention of salt and water by the kidneys, thus further aggravating the edema.

The genesis of the **hyperlipidemia** is more obscure. Presumably, hypoalbuminemia triggers increased synthesis of lipoproteins in the liver. There is also abnormal transport of circulating lipid particles and impairment of peripheral breakdown of lipoproteins.

Pathology of the kidney in nephrotic syndrome

Gross: The kidneys are enlarged and pale due to edema, and may have a yellowish tinge due to presence of lipid resorbed from the urine into the renal tubular epithelium.

Microscopic

1. **The glomeruli show** the pathological features of the cause of nephrotic syndrome as seen by light microscopy, immunofluorescence and electron microscopy.
2. **The tubules show:**
 - a. **Hyaline droplet degeneration** of the epithelium of the convoluted tubules due to resorption of protein from the urine.
 - b. **Vacuolar degeneration** of the epithelium of the convoluted tubules due to resorption of lipids from the urine.
 - c. **Protein casts** within the tubular lumen.
3. **The interstitial tissue shows** variable edema.

Electron microscope: All cases show fusion "effacement of foot processes of the podocytes".

Lesions causing nephrotic syndrome:

1- Minimal change Disease:

This occurs most commonly in children. (1-4)

Pathogenesis:

It is not known; proteinuria has been attributed to a circulating, possibly T cell-derived, factor that causes podocyte damage and effacement of foot processes. *Factor that causes podocyte damage and effacement of foot processes*

Microscopic: no changes are seen in the glomeruli (Nil disease). The tubules and interstitial tissue show the changes already described under the nephrotic syndrome (Fig. 7.6). *as nephrotic syndrome*

Immunofluorescence: reveals negative findings.

Electron microscopy: reveals only fusion of foot processes of the podocytes (foot process disease). *- no deposits*

Clinical and laboratory findings:

Nephrotic syndrome with highly selective proteinuria (i.e. essentially an albuminuria).

Course and prognosis:

- The prognosis is good, particularly in children, with prolonged remission or even permanent cure occurring spontaneously or in response to steroid therapy. *selective proteinuria (albuminuria)*
- Only rare cases progress to chronic renal failure.

2- Focal segmental glomerulosclerosis:

FGS may be primary (idiopathic) or secondary to HIV infection or as a secondary event as in IgA nephropathy. *congenital or acquired*

Pathogenesis: It is unknown. Injury to the podocytes is thought to represent the initiating event of primary FGS. The deposition of hyaline masses in the glomeruli represents the entrapment of plasma proteins and lipids in foci of injury where sclerosis develops. *in the glomeruli*

Microscopic: This is characterized by the presence of sclerotic segments in a variable number of glomeruli together with variable tubular atrophy and interstitial fibrosis. (Fig. 7.7). *hyaline masses, tubular*

Immunofluorescence: reveals non-specific trapping of immunoglobulins, usually IgM and C3 in the sclerotic glomerular segments.

Electron microscopy: reveals only fusion of foot processes of the podocytes. *no deposits, detachments of podocytes*

Clinical:

- Most patients present clinically with nephrotic syndrome, however some *non-selective*

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cases present with nephrotic/nephritic syndrome.

- Proteinuria is nonselective
- The condition is resistant to steroids and the prognosis is unfavourable.

3- Membranous nephropathy:

It is a slowly progressive disease, mostly seen in adults.

Pathogenesis:

a- It is a form of chronic immune complex GN induced by antibodies reacting in situ to endogenous or planted glomerular antigens. Antigen-antibody complexes activate the complement which damages mesangial cells and podocytes.

b- Secondary membranous glomerulonephritis occurs in the course of viral B hepatitis, schistosomiasis, malaria, syphilis, some malignant tumours, gold salt therapy and non-steroidal anti-inflammatory drugs.

Microscopic: There is diffuse uniform thickening of glomerular capillary walls (Fig. 7.8).

Immunofluorescence: reveals granular deposits of IgG and complement along the GBM (Fig. 7.9).

Electron microscopy: reveals subepithelial electron dense deposits separated by outward projections of the GBM termed "spikes". More advanced stages of the disease show actual thickening of the GBM with disappearance of deposits and spikes.

Course and prognosis:

- It does not usually respond to corticosteroid therapy.
- It shows an indolent course.
- Proteinuria is nonselective and persists in greater than 60% of patients.
- About 40% suffer of progressive disease terminating in renal failure after 2 to 20 years.
- An additional 10% to 30% have a more benign course with partial or complete remission of proteinuria.

4- Membranoproliferative glomerulonephritis (MPGN):

- o This occurs in all ages, particularly late childhood.
- o There are 2 types of MPGN; type I and II.

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Etiology

- ① **Type I MPGN** may be caused by immune complexes. The antigen involved is not known. Some cases are associated with hepatitis B viral infection, SLE and extra-renal infections (secondary MPGN).
- ② **Type II MPGN (dense deposit disease)** appears to be due to excessive complement activation. Some patients have autoantibody against C3 (C3 nephritic factor). This factor leads to uncontrolled cleavage of C3 and activation of alternative complement pathway resulting in marked reduction in C3 (hypocomplementaemic GN).

Microscopy The glomeruli are large and show:

- Hypercellularity due to proliferation of mesangial and endothelial cells.
- Increased mesangial matrix with consequent accentuated lobulation.
- Thickening of GBM; often shows partial or circumferential double contours "Tram Track" appearance (Fig. 7.10).

NB: The subendothelial immune complex deposits and mesangial cell interposition cause thickening of GBMs and splitting creating a tram track appearance.

Immunofluorescence

- **Type I MPGN:** IgG and C3 are deposited in granular pattern along GBM, and early complement components are present.
- **Type II MPGN:** GBM shows granular deposits for C3. Immunoglobulins and complement components earlier than C3 are not found.

Electron microscopy

- **Type I MPGN:** Subendothelial electron dense deposits.
- **Type II MPGN:** Intramembranous dense deposits (GBM appears irregular, ribbon-like and extremely dense structure).

Clinical and laboratory findings:

1. Most cases present with nephrotic syndrome.
2. Few cases present with nephritic syndrome or asymptomatic proteinuria.

Course and prognosis:

- The prognosis of MPGN type I is generally poor.
- 40% progress to end-stage renal failure.
- Dense deposit disease carries an even worse prognosis.

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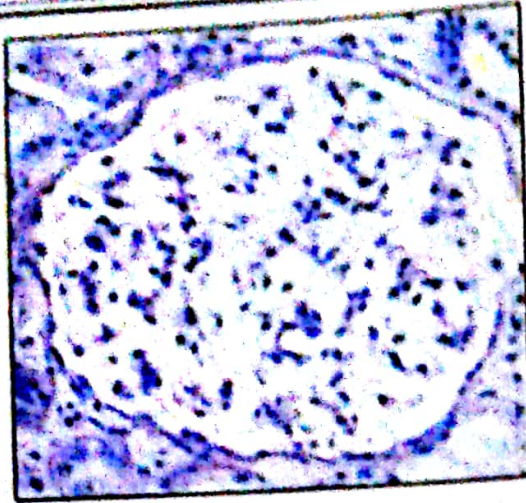


Fig. 7.6: Minimal change GN

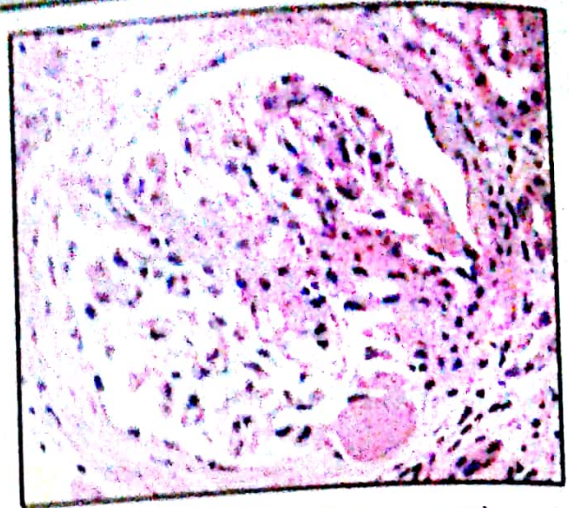


Fig. 7.7: Focal & segmental glomerulosclerosis

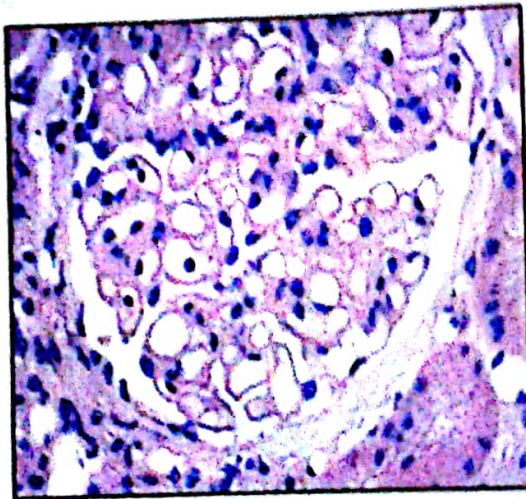


Fig. 7.8: Membranous GN

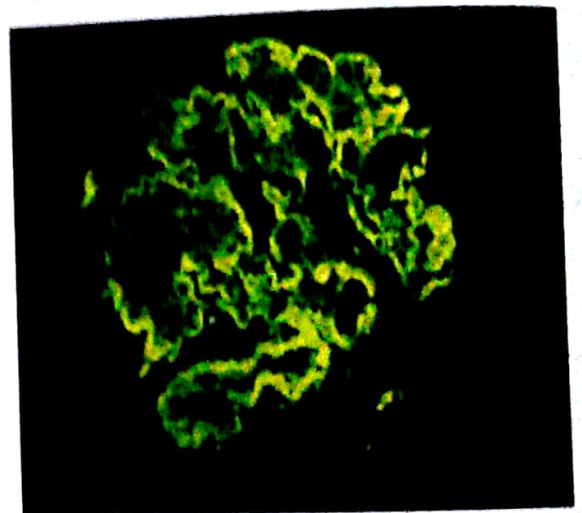


Fig. 7.9: Membranous GN: IF granular deposits of IgG and C3 along the GBM

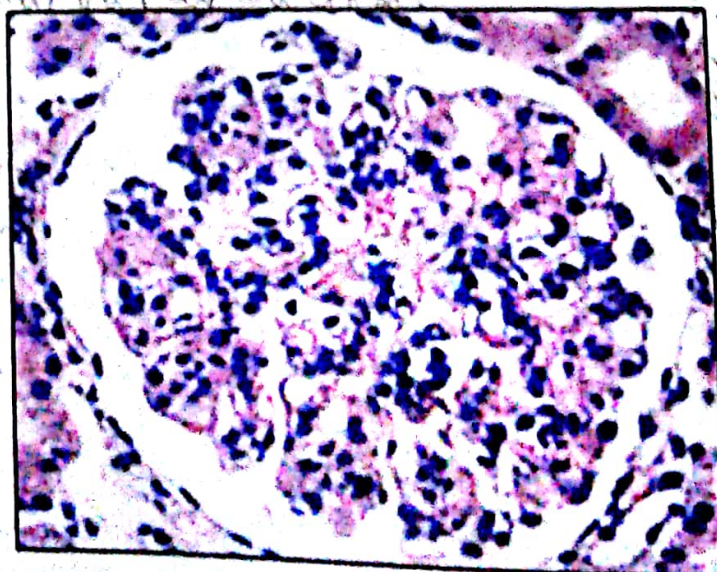


Fig. 7.10: MCGN

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Table 7.2: Differences between type I and II membranoproliferative GN

	Type I MPG (2/3 of cases)	Type II MPGN
Cause	Circulating immune complexes	C3 nephritic factor
LM	The glomeruli are large, Lobulated and show proliferation of mesangial cells & leukocytes. The GBM is thickened (<i>Fig. 7.10</i>)	
	The GBM shows a double contour or "tram track"	--
EM	Subendothelial electron-dense deposits	Intra-membranous deposits
IF	Subendothelial granular deposits of C3 & IgG (immune complex)	C3 deposits as irregular and segmental linear foci in the GBM & in the mesangium. IgG is usually absent

Nephritic Syndrome:

It is a clinical complex, usually of acute onset, characterized by:

- *Hematuria* with red blood cell casts in the urine
- *Oliguria* and azotemia
- *Hypertension*.

Although there may also be some proteinuria and even edema, these are usually not as severe as in the nephrotic syndrome.

Pathogenesis of nephritic syndrome:

- The lesions that cause the nephritic syndrome have in common proliferation of the cells within the glomeruli, accompanied by a leukocytic infiltrate.
- This inflammatory reaction injures the capillary walls, permitting escape of red cells into the urine, and induces hemodynamic changes that lead to a reduction in the GFR,
- The reduced GFR is manifested clinically by oliguria, reciprocal fluid retention, and azotemia.
- Hypertension is probably a result of both the fluid retention and some augmented renin release from the ischemic kidneys.

Causes of nephritic syndrome:

- **Primary GN:**
 - I- Acute diffuse proliferative GN
 - II- Rapidly progressive (crescentic) GN
 - III- IgA nephropathy (Berger's disease).
- Systemic causes as SLE and Henoch Schoenlein purpura.

I- Acute post infectious (poststreptococcal) glomerulonephritis:

This is mostly seen in **children** and usually develops **1 - 2 weeks** following infection of the upper respiratory tract by group A β -haemolytic streptococci. Occasional cases may follow infection by staph aureus or viruses.

Pathogenesis:

- It is an immune complex disease; tissue injury is **caused** primarily by **complement activation by the classic pathway**.
- The **antigens** are most likely streptococcal proteins that **activate alternative complement pathway**.
- It is not clear if immune complexes are formed mainly in the circulation or in situ.

Gross: The **kidneys** may be slightly **enlarged** and **pale** due to edema.

Microscopic: *interstitial tissue - edematous*

- All **glomeruli** are affected in a diffuse manner. They are **enlarged** and **hypercellular** due to **proliferation of endothelial and mesangial cells** as well as **infiltration by neutrophils and monocytes**. There is obliteration of many of capillary lumina by swollen and proliferated endothelial cells.

- **Tubules** *acute tubulonephritis* contain **red cell casts**. **Blood vessels** are **unremarkable** (Fig. 7.11).

Immunofluorescence reveals **granular fluorescence** of GBM and mesangium for immunoglobulins (IgG) and complement components. *C3, IgG, C5b-9, C3a, C5a*

Electron microscopy reveals discrete **subepithelial electron dense deposits** known as "**humps**". *subepithelial electron dense deposits*

Clinical and laboratory findings:

1. **Fever and malaise.**
2. Mild to moderate **hypertension** due to **decreased renal blood flow**.
3. Mild to moderate **increase of blood urea** due to decreased glomerular filtration rate as a result of decreased renal blood flow.
4. The urine is decreased in volume (**oliguria**), gross **hematuria** (**smoky urine**) and shows **increased specific gravity**, mild **proteinuria** (usually less than 1 gm), many R.B.C.'s and red cell casts.

5. **Elevated ASO titer**
6. **Low serum complement levels**

Course and prognosis:

⊙ In children:

- Over **95% recover completely within about 2 weeks**, either spontaneously or with conservative therapy.
- The **remainder die during the acute attack by acute renal failure or complications of hypertension**, get progressively worse and develop a rapidly progressive glomerulonephritis (see later).
- Progress quietly and slowly to chronic glomerulonephritis. *To R.P.G.N*

⊙ In adults, the disease is less benign; **only about 60% of cases recover completely**.

II- Rapidly progressive (Crescentic) glomerulonephritis:

It is a clinical syndrome characterized by rapid deterioration of the renal function with features of nephritic syndrome and histologically by the presence of crescents.

Pathogenesis:

Cause: idiopathic

Crescentic glomerulonephritis is classified into 3 types:

1. **Antiglomerular basement membrane antibody mediated crescentic GN**; characterized by linear deposits of IgG and C₃ along the glomerular capillary wall. *Good prognosis*
2. **Immune complex mediated crescentic GN**; such as poststreptococcal GN, SLE, **IgA nephropathy** and **Henoch Schonlein purpura** as well as some idiopathic cases characterized by granular deposits along the glomerular capillary wall and/or mesangium.
3. **Pauci-immune crescentic GN**: Characterized by **lacking anti-glomerular basement membrane antibodies** or immune-complex by immunofluorescence and electron microscopy; as **polyarteritis nodosa** and **Wagner's granulomatosis**. *+ve ANCA*

Gross: The **kidneys** are slightly **enlarged** and **pale** with **petechial haemorrhages in the cortex**. *2/3 C*

Microscopic:

- The striking feature is the presence of **large epithelial crescents in over 50% of glomeruli**, as a result of proliferation of the capsular epithelium.
- The crescents may be **cellular, fibrocellular or fibrous (Fig. 7.12)**.

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• The glomeruli show:

- In anti-GBM disease; **segmental necrosis**.
- Immune complex mediated crescentic GN: segmental necrosis and evidence of underlying disease.
- In Wagner's granulomatosis, segmental necrosis with haemorrhage and fibrinoid necrosis of the blood vessels.
- **The tubules contain protein or red cell casts.**
- **The interstitial tissue is oedematous.**
- **Blood vessels may show changes of malignant hypertension.**
- With the advance of disease, some of the crescents and the necrotic glomerular segments undergo sclerosis.
- This is eventually followed by tubular atrophy and interstitial fibrosis.

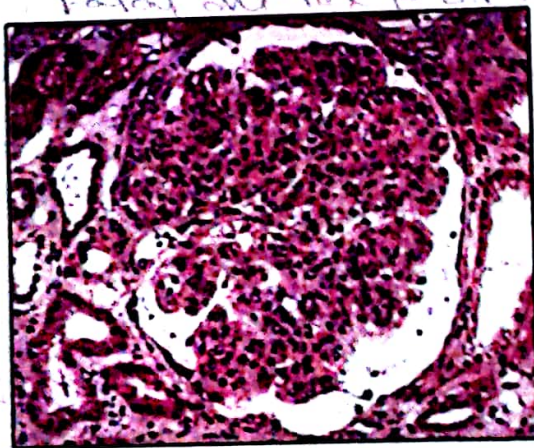


Fig. 7.11: Diffuse proliferative GN

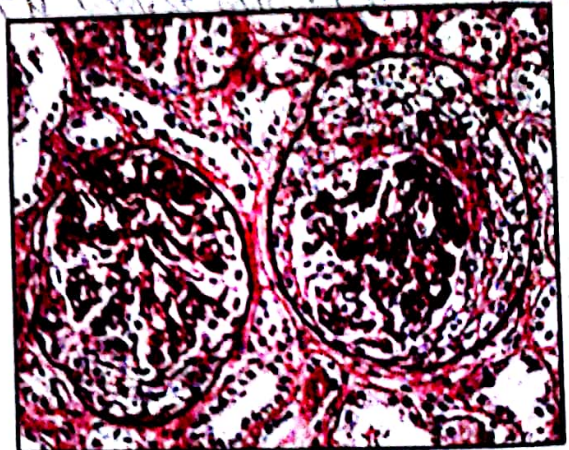


Fig. 7.12: Crescentic GN

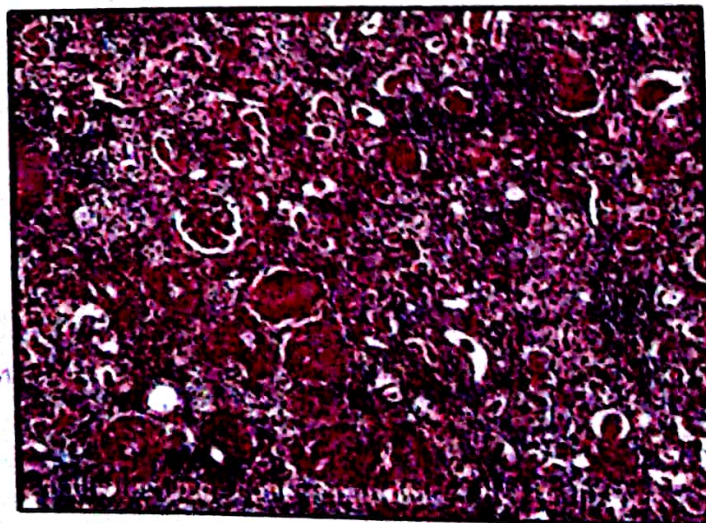


Fig. 7.13: Chronic kidney disease

Goodpasture's
ca by subcutaneous
haemorrhage and
Rapidly progressive
GN
affects young adult
Sex: males
Cause:
exposure to hydrocarbon
solvents, drugs such
as penicillin.
anti-GBM Ab
Mediated
- auto anti bodies react with BM-tubule and glomerul
- haemorrhage

III- IgA Nephropathy:

This condition usually affects children and young adults and begins as an episode of gross hematuria that occurs within 1 or 2 days of a nonspecific upper respiratory tract infection.

- Typically, the hematuria lasts several days and then subsides, only to recur every few months.
- Common at ages 10-29 years, usually males
- IgA nephropathy is one of the most common causes of recurrent microscopic or gross hematuria and is the most common glomerular disease revealed by renal biopsies worldwide

Pathogenesis:

- The pathogenic hallmark is the deposition of IgA in the mesangium due to abnormality of IgA production and clearance or abnormality in glycosylation of IgA.
- May be secondary to liver diseases (secondary IgA)
- IgA aggregates in mesangium, activate alternative complement pathway.

Microscopic: The lesions in IgA nephropathy vary considerably.

The glomeruli may be normal or may show mesangial widening and segmental inflammation confined to some glomeruli (focal proliferative GN); diffuse mesangial proliferation (mesangioproliferative); or (rarely) overt crescentic GN.

Immunofluorescence: The characteristic picture is mesangial deposition of IgA and smaller amounts of IgG or IgM.

Electron microscopy: confirms the presence of electron-dense deposits in the mesangium.

Course and prognosis:

- Good in most patients
- Poor prognostic features: Crescents, prominent arteriolar hyalinization, older age, heavy proteinuria and hypertension

Chronic kidney disease:

It is the result of progressive scarring resulting from any type of kidney disease. This eventually results in an end-stage kidney where glomeruli, tubules, interstitium and vessels are sclerosed.

Gross: Classically, the kidneys are symmetrically contracted, and their surfaces are red-brown and diffusely granular.

Microscopic

- Advanced scarring of the glomeruli, sometimes to complete sclerosis.
- Marked **interstitial chronic inflammatory infiltrate and fibrosis**.
- Atrophy of many of the tubules in the cortex.
- The **small and medium-sized arteries** are **thick-walled**, with **narrowed lumina**, secondary to hypertension.
- Such damaged kidneys have been designated **end-stage kidneys**.

Clinical Course:

- It may develop insidiously and discovered late, after the onset of renal insufficiency.
- Frequently, there is **proteinuria**, **hypertension**, or **azotemia**, *polyuria*
- Disease-specific findings as nephrotic syndrome, microscopic **hematuria** may be present. *protein cast, hyaline cast.*
- Without treatment, the **prognosis is poor**; progression to uremia and death is the rule.

Systemic diseases with renal manifestations (secondary GN):

1. **Diabetic glomerulosclerosis:**

- Diabetes mellitus is a major cause of renal morbidity and mortality.
- It may lead to **diabetic glomerulosclerosis**, **renal arteriolar sclerosis**, **pyelonephritis** and **papillary necrosis**.
- Diabetic glomerulosclerosis occurs in patients with long standing diabetes mellitus for 12 years or more. It leads to **proteinuria**, **nephrotic syndrome** or **chronic renal failure**, and may take the form of:
 1. **Diffuse glomerulosclerosis** in which there is **diffuse increase of mesangial matrix** and thickening of **glomerular basement membrane**
 2. **Nodular glomerulosclerosis** (**Kimmelstiel-Wilson lesion**) in which one or more **hyaline nodules** are present in the **mesangium**, containing **lipid and fibrin** (Fig. 7.14). *insidious lesion - fibrin cap - eosinophilic focal thickening peripheral capillary wall*

2. **Amyloid nephropathy:**

Amyloidosis of the kidney is the most common and most serious feature of the disease. **Amyloid material** is a **non-soluble fibrillary protein made up of misfolded proteins** (which are soluble in the normal folded pattern). The kidney is affected in primary and secondary systemic amyloidosis as well as in familial forms. The patient **presents with proteinuria or the nephritic syndrome**. The cause of proteinuria is **destruction of GBM structure by amyloid fibrils**. *capillary wall drops - eosinophilic thickening of basement membrane*

3. **Lupus nephritis:**

The kidneys are involved in most cases of systemic lupus erythematosus giving rise to a heterogeneous group of glomerular lesions and clinical presentations.

Pathogenesis: The mechanism of renal injury in lupus nephritis is due to deposition of DNA-antiDNA complexes in glomeruli that may provoke proliferation of endothelial, mesangial and epithelial cells, and may cause even necrosis.

The clinical manifestations include recurrent haematuria, the nephritic syndrome, the nephrotic syndrome, hypertension and chronic renal failure. Renal failure is the cause of death in over one-third of patients with systemic lupus erythematosus.

Immunofluorescence reveals granular fluorescence of glomerular capillary walls and mesangium for most immunoglobulins and all complement components.

Electron microscopy shows large subendothelial and mesangial electron dense deposits, the former corresponding to the wire loops seen by light microscopy.

Table.6.2: ISN/RPS classification of lupus nephritis.

Classification of lupus nephritis	
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV*	Diffuse lupus nephritis ($\geq 50\%$ of glomeruli)
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

***Class IV** is the most serious and commonest form of lupus nephritis. The lesion involves more than 50% of glomeruli (diffuse). The glomeruli show global hypercellularity, capillary wall thickening, wire loop appearance, leucocytes and occasionally crescents (Fig. 7.15).

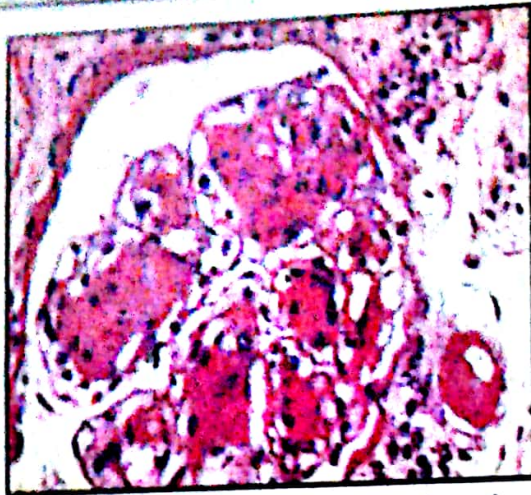


Fig. 7.14: Diabetic glomerulosclerosis

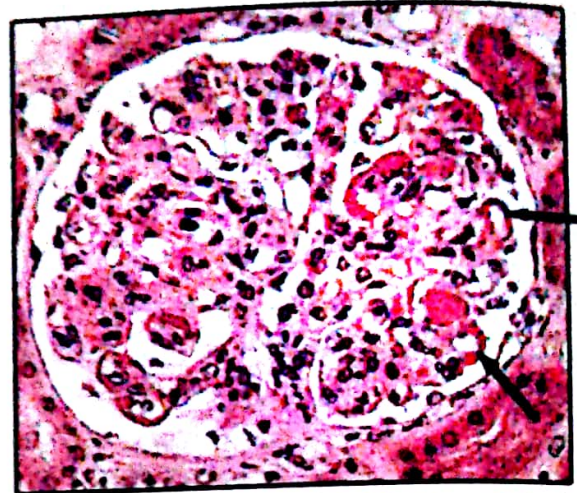


Fig. 7.15: Lupus nephritis Class IV with wire loop appearance (arrows)

Tubulointerstitial nephritis (TIN):

Pyelonephritis:

It is a **suppurative inflammation** of the pelvicalyceal system and the renal parenchyma; it is **usually bilateral**.

Causative organisms include *E. coli*, *B. proteus*, *B. pyocyaneus*, *Aerobacter*, *Klebsiella* and *Strept. faecalis*.

Predisposing factors:

1. **Obstruction** to the urinary tract **with stasis of urine**.
2. **Vesicoureteric reflux**: Normally, the urine does not **ascend** along the ureters during micturition owing to the **oblique course** of the intravesical portion of the ureter, which **provides a sphincter-like effect during contraction of the bladder**. If this effect is disturbed due to congenital or acquired reasons, the urine will ascend along the ureters and may even reach the kidneys during bladder emptying.
3. **Bilharziasis**.
4. **Instrumentation of the urinary tract**.
5. **Diabetes mellitus** due to generalized susceptibility to infection.
6. **Female sex** due to short urethra.
7. **Pregnancy** due to hormonal **relaxation of smooth muscle** and pressure of the gravid uterus.

Routes of infection:

1. **Ascending infection** from the lower urinary tract.
2. **Blood borne infection**.

lymphatic from GIT

Gross: The **pelvicalyceal system** is **acutely inflamed**, and the **renal parenchyma** shows **multiple foci of suppuration** which appear as **yellow streaks radiating from the renal papillae**, to expand into "abscesses" in the **cortex** (Fig. 7.16).

Microscopic:

- The **pelvicalyceal system** is **acutely inflamed**.
- The **renal parenchyma** is **congested** and **infiltrated by neutrophils** which collect in the **interstitial tissue** or within the **tubular lumen** to form **abscesses**.

Clinical features:

- **Frequency and dysuria** (lower urinary tract infection).
 - **Fever, rigors, pain and tenderness over the loins** (pyelonephritis).
 - The **urine** shows: **protein** and **RBC cellular casts**.
- It may **resolve**, progress to **chronic pyelonephritis** or to **acute renal failure**.

b- Chronic pyelonephritis:

Gross:

1- Chronic Obstructive Pyelonephritis:

- Obstruction leads to **recurrent renal inflammation and scarring**.
- The disease can be **bilateral**, as with **congenital anomalies** of the urethra, or **unilateral**, as occurs with **calculi** and **unilateral obstructive lesions** of the ureter.

2- Chronic Reflux-Associated Pyelonephritis:

- This is more common. It results from **superimposition** of a **urinary tract infection** on **congenital vesicoureteral reflux** and **intrarenal reflux**.
- Reflux may be **unilateral** or **bilateral** leading to **chronic renal insufficiency**.

Gross: *small sized kidney, irregular outer surface due to retraction.*
 ➤ One or both kidneys may be involved, either **diffusely** or in **patches**. *the capsul*
 ➤ The kidneys are not **equally damaged** (*uneven scarring*).
 ➤ The **scarring** involves the **pelvis** or **calyces**, or both, leading to **papillary blunting** and **marked calyceal deformities**. *distorted pelvis, calyceal deformities*

Microscopic:

- **Uneven interstitial fibrosis** and an **inflammatory infiltrate** of **lymphocytes**, **plasma cells**, and occasionally **neutrophils**.

Periglomerular fibrosis, dilated tubules containing hyaline cast (the fluid portion), thickened BVE (basal membrane), chronic inflammatory cell infiltrate in interstitium, lymphoplasmic, no typical abscesses.

Chapter 7: Diseases of the kidney

- Dilation of tubules, with **atrophy of the lining epithelium**. Many of the tubules contain pink, **PAS-positive casts**, giving the appearance of thyroid tissue (**thyroidization of the tubules**).
- Often, neutrophils are seen within tubules.
- Inflammation and fibrosis involve the calyceal mucosa and wall
- **Arteriosclerosis** caused by the frequently **associated hypertension**.
- Glomerulosclerosis that usually develops as a secondary process caused by nephron loss.

Clinical features:

- ☐ Chronic renal failure with uremia and **hypertension**.
- ☐ Pyelography shows **destruction of calyces**.
- ☐ Active cases show **bacteria, polymorphs, casts and protein in urine**.

Tuberculous pyelonephritis:

- ☐ It is a secondary TB.
- ☐ It occurs due to **hematogenous spread** of infection, usually from the lung or ascending infection from TB of the genitourinary system.
- ☐ The renal lesion may be TB pyelonephritis or military TB

Gross:

- It is often **bilateral**, involving the **medulla with replacement** of the **papillae by caseous material**.
- Obstruction may result in TB pyonephrosis.

Microscopia: Caseating tuberculous granulomatous inflammation.

Clinical: Sterile pyuria, microscopic hematuria and mild proteinuria.

Drug-induced interstitial nephritis:

In this era of antibiotics and analgesics, drugs have emerged as important causes of renal injury. Two forms of TIN caused by drugs are discussed below.

1- Acute drug-induced interstitial nephritis:

Acute TIN most frequently occurs as an adverse reaction to: **synthetic penicillins (methicillin, ampicillin)**, other synthetic antibiotics (**rifampin**), diuretics (**thiazides**), nonsteroidal anti-inflammatory agents, and numerous other drugs (**phenindione, cimetidine**).

Pathogenesis

- An immune mechanism is suggested; **the drugs act as haptens** that during secretion by tubules, covalently bind to some cytoplasmic or extracellular component of tubular cells and become immunogenic.

Chapter 7: Diseases of the kidney

- The resultant **tubule-interstitial injury** is then caused by **IgE- and cell-mediated immune reactions** to tubular cells or their basement membranes.
- The mononuclear or granulomatous infiltrate, together with positive skin tests to drugs, suggests a **T cell-mediated (type IV) hypersensitivity reaction**.

2-Analgesic nephropathy:

- Individuals who consume large quantities of analgesics may develop **chronic interstitial nephritis**, often associated with **papillary necrosis**.
- It usually occurs in patients consuming combination of **phenacetin, aspirin, acetaminophen**, for long periods.

Pathogenesis:

- Renal papillary necrosis is the initial event, and the **interstitial nephritis** in the overlying renal parenchyma is a secondary phenomenon.
- **Acetaminophen**, a phenacetin metabolite, injures cells by both **covalent binding** and **oxidative damage**.
- **Aspirin** inhibits the vasodilatory effects of prostaglandin, **predisposing** the papilla to ischemia.
- Thus, the **papillary damage** may be caused by a combination of **direct toxic effects of phenacetin metabolites** as well as **ischemic injury** to both tubular cells and vessels.

Gross: The **necrotic papillae** appear **yellowish brown**, as a result of the **accumulation of breakdown products of phenacetin and other lipofuscin-like pigments**. Later on, the **papillae may be sloughed off**, and drop into the pelvis.

Microscopic: The papillae show **coagulative necrosis**.

Clinical Course: Common clinical features of analgesic nephropathy include **chronic renal failure, hypertension, and anemia**.

Acute tubular injury (ATI):

ATI is the most common cause of acute renal failure. Its clinical manifestations are **oliguria, uremia, and signs of fluid overload**.

ATI results from ischemic or toxic injury to renal tubules, associated with intrarenal vasoconstriction resulting in **reduced GFR** and diminished delivery of oxygen and nutrients to tubular epithelial cells.

a- **Anoxic tubular necrosis may be caused by:**

1. **Mismatched blood transfusion.**
2. **Crush injuries.**

3. Burns

4. Shock

b. **Toxic tubular necrosis may be caused by:**

1. **Poisons** e.g. mercuric chloride, phosphorous, carbon tetrachloride, insecticides.

2. **Some drugs** e.g. gentamicin, amphotericin B.

Microscopic: ATN is characterized by **necrosis of tubular epithelial cells** (typically the **proximal tubules**), **proteinaceous casts in distal tubules**, and **interstitial edema**. *neutrophilic infiltration* *due to debris of necrotic cells*

Vascular diseases of the kidney

A-Renal artery stenosis: This leads to secondary hypertension.

Causes: **Atherosclerosis**, **arterial fibromuscular dysplasia**, **vasculitis**, or **radiation injuries**. *Etiology - try MGN due to FGF19 production*

B-Kidney of hypertension:

1. **Benign nephrosclerosis:** Is the term used for abnormalities of the kidney induced by benign hypertension.

Gross:

- Both kidneys are reduced in size (primary **contracted kidney**).
- The **outer surface** is **finely granular** and may show **small cysts**.
- The **cut surface** shows **irregular atrophy of the cortex** with **loss of demarcation between cortex and medulla**. *irregular irregularity*

Microscopic: There is **hyaline arteriosclerosis** (Fig. 7.17).

- **Large muscular arteries** show **fibroelastic hyperplasia**.
- **Arterioles** show **thickening and hyalinization** of their walls with **luminal narrowing** leading to **diffuse ischemic atrophy of the nephrons**.

NB! Benign nephrosclerosis alone rarely causes severe damage to the kidney. However, all patients show **loss of concentrating ability** or a **diminished GFR**. A mild degree of **proteinuria** is a frequent finding.

2. **Malignant nephrosclerosis:**

It may arise **without preexisting hypertension**, or it may appear suddenly in a person who had mild hypertension.

Gross: The kidney shows **petechial hemorrhages** on the cortical surfaces (**flea-bitten appearance**). *enlarged kidney*

Microscopic: There is **fibrinoid necrosis of arterioles** (**necrotizing arteriolitis**), **hyperplastic arteriosclerosis** (**Onion-skin appearance**), and **necrotizing glomerulitis** (Fig. 7.18). *small vessels pr. between tufts*

Chapter 7: Diseases of the kidney

Clinical course:

- It is characterized by **papilledema**, **encephalopathy**, **cardiovascular abnormalities** and **renal failure**.
- **Increased intracranial pressure** causes headache, nausea, vomiting, and visual impairment.
- About 50% of patients survive at least 5 years.
- 90% of deaths are caused by uremia and **10%** by **cerebral hemorrhage** or **cardiac failure**.



Fig. 7.16: Acute pyelonephritis

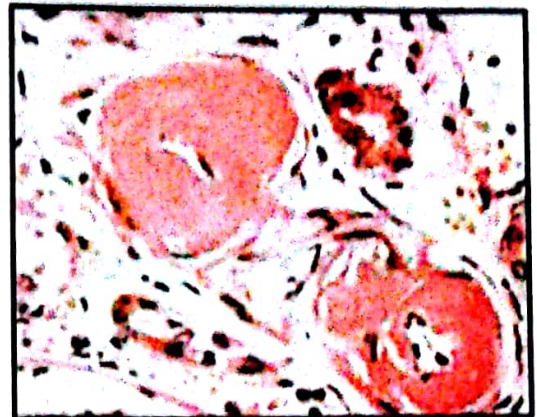


Fig. 7.17: Benign hypertension
Hyaline thickening of the wall

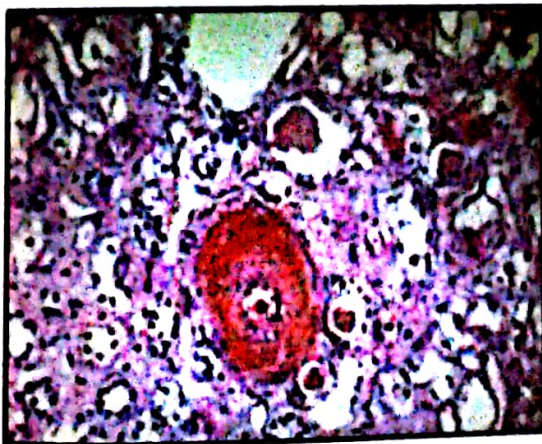
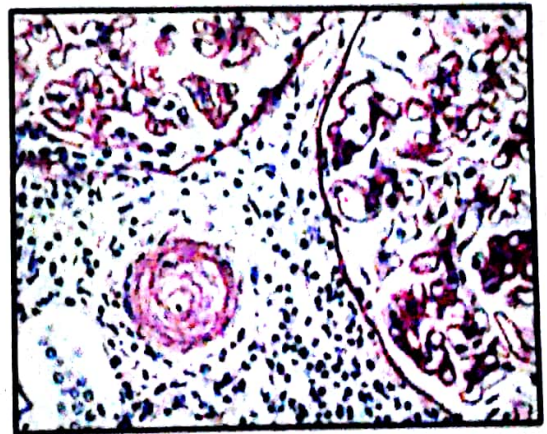


Fig. 7.18: Malignant hypertension
(a) Fibrinoid necrosis



(b) Hyperplastic onion skin lesion

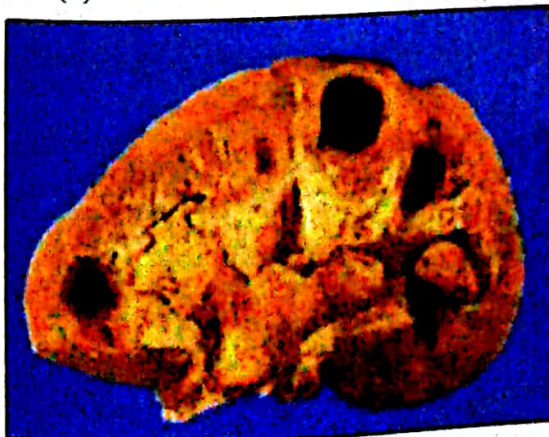


Fig. 7.19: Renal stag-horn stone



Fig. 7.20: Hydronephrosis

Renal calculi:

Renal urolithiasis, is calculus formation at any level in the urinary collecting system, but most often the calculi arise in the kidney.

Urinary calculi are formed by the precipitation of inorganic urinary constituents with a small amount of organic material.

Factors favoring stone formation include (Table. 7.3):

- **Increased urinary concentration** of the stone's constituents so that it exceeds their solubility in urine (supersaturation).
- **Changes in urine pH**, bacterial infection and Bilharziasis
- **In avitaminosis A**, the **desquamated cells** from metaplastic epithelium of the collecting system **act as nidi for stone formation**.
- **Stasis**. site: pelvis, ureter, RUB
- **Diminished factors inhibiting mineral deposition**, (pyrophosphate, mucopolysaccharides, diphosphonate, nephrocalcin)

Types of renal stones:

1. **Oxalate stones**: These are **primary** stones, small, often multiple, with rough spiky surface, hard in consistency and dark brown or black in colour. They are radio opaque.
2. **Urate stones**: These are **primary** stones, with smooth surface, yellow brown in colour, usually small, may be Large stag-horn, hard in consistency and radio translucent.
3. **Phosphate stones**: They are usually preceded by infection which turns the pH of urine alkaline thus helping precipitation of phosphate salts (secondary stone). They are moderately large and branched (stag-horn stone "Fig. 7.19"), smooth, friable, chalky white and radio-opaque.
4. **Cystine stones**: They are very rare and pale yellow white in colour.

Effects and complications of urinary stones: –

1. **Renal colic**: occurs commonly with small stones while passing down the ureter.
2. **Haematuria**: It is common with **oxalate stones**, due to the rough surface which cause injury to the mucosa.
3. **Infection**: As cystitis, acute and chronic pyelonephritis.
4. **Obstruction** leading to:
 - a- **Hydroureter** and **hydronephrosis**. It occurs if the obstruction is intermittent or incomplete.

4. **Calculous atrophy** It occurs if the obstruction is complete leading to marked atrophy of the kidney.
5. **Chronic irritation** of the epithelium leading to **squamous metaplasia**.
6. **Trauma to the mucosa**, may lead to stricture formation due to healing by fibrosis (e.g. in the ureter and urethra).
7. **Malignant transformation** into carcinoma of the urinary bladder or the pelvis of the kidney due to chronic irritation and infection.

Table 7.3: Prevalence and causes of renal stones.

Stone	Distribution
1- Calcium oxalate and/or calcium phosphate • Idiopathic hypercalcaemia (50%) • Hypocalcaemia and hypercalcaemia (10%) • Hyperoxaluria (5%) • Hyperuricaemia (20%) • No known metabolic abnormality (15% - 20%)	80%
2- Struvite (Mg, NH₃, Ca, PO₄) • Renal infection	10%
3- Uric acid • Associated with hyperuricaemia • Associated with hyperuricosuria • Idiopathic (50% of uric acid stones)	6-7%
4- Cystine	1-2%
5- Others or unknown	±1-2

Table 7.4: Main types of stones

	Oxalate	Urate	Triple phosphate
Type	Primary	Primary	Secondary
Site	Pelvis, calyces and bladder		
Size & No	Small, multiple	Usually small, may be Large stag-horn.	Large stag-horn.
Colour & consistency	Black, spiky, hard	Yellow brown, smooth, hard	Chalky white, friable & smooth.
Radio-opacity	Opaque	Liacent	Opaque

Chapter 7: Diseases of the kidney

Hydronephrosis

It is the dilatation of the pelvis and calyces of the kidney, leading to pressure atrophy of the kidney tissue. It is due to gradual, incomplete or intermittent obstruction to the flow of urine.

Gross: The kidney is enlarged in size, the outer surface may be lobulated. The pelvis and calyces are dilated with atrophy and fibrosis of the renal tissue (Fig. 7.20). *communicated with*

Microscopic: There is atrophy of the tubules and the glomeruli with fibrosis. *pyelonephritis is common*

Causes of hydronephrosis:

(1) **In the urethra:** Leading to bilateral hydroureter and hydronephrosis.

a- Nodular hyperplasia of the prostate and cancer prostate.

b- Stricture of the urethra whether congenital, traumatic or due to gonorrhea, stones

(2) **In the urinary bladder:** If the cause is in the bladder neck it will cause bilateral hydronephrosis, but elsewhere it will cause unilateral hydronephrosis.

a- Bilharzial stricture: Either in the ureteric orifice or causing bladder neck obstruction.

b- A large stone in the urinary bladder.

c- Tumours: As carcinoma or papilloma of the urinary bladder.

(3) **In the ureter:** Leading to unilateral hydroureter and hydronephrosis:

a- Congenital: causes as congenital stricture or aberrant renal artery pressing the ureter.

b- Stone in the ureter.

c- Bilharzial stricture.

d- Tuberculosis of the ureter.

e- Endometriosis with pelvic lesions, followed by scarring.

f- Cancer cervix in females infiltrating the ureter.

g- Ectopic kidney leading to kinking of the ureter.

h- Retroperitoneal fibrosis: It is an idiopathic disease leading to the formation of dense fibrous tissue extending from the lower part of the vertebral column and extends laterally to involve the ureter.

(4) **In the kidney:** which may be due to stones and tumours. It usually leads to unilateral hydronephrosis.

Renal failure

Acute renal failure:

It is a syndrome characterized by oliguria (a 24 hour urine volume less than 400 ml.) and a rapid onset of azotaemia (elevation of blood urea nitrogen and creatinine levels).

Causes:

1. Severe reduction in glomerular filtration by:
 - a- **Prerenal causes:** Acute circulatory failure.
 - b- **Postrenal causes:** Complete prolonged obstruction of urethra or both ureters.
 - c- **Renal causes:** Acute and rapidly progressive glomerulonephritis.
2. **Acute failure of tubular epithelium,** due to:
 - a- **Acute tubular injury.**
 - b- **Papillary necrosis.** *necrotizing papillitis*
 - c- **Acute pyelonephritis.** *bilateral cortical necrosis*

Chronic renal failure:

Is the end stage of a number of renal diseases and manifests itself as uraemia (azotaemia with a constellation of persistent clinical signs and symptoms).

Causes: *uric acid - xanthine sclerosis*

- 1- **Chronic glomerulonephritis,**
 - 2- **Bilateral chronic pyelonephritis.**
 - 3- **Polycystic disease,**
 - 4- **Bilateral hydronephrosis,**
 - 5- **Systemic lupus erythematosus.**
 - 6- **Amyloidosis.**
 - 7- **Gout.**
 - 8- **Analgesic nephropathy** (Nonsteroidal anti-inflammatory drugs).
 - 9- **Irradiation injury,**
 - 10- **Hypertension,** especially the malignant type.
 - 11- **Diabetic nephropathy.**
 - 12- **Renal tuberculosis** (when bilateral).
- Handwritten notes:*
nephrotic syndrome
acute tubular necrosis
peripheral neuropathy
chronic pyelonephritis
fibrinous pericarditis
pleurisy
uraemic pneumonitis
etc.

Pathologic changes in renal failure:

- a- Changes in the kidney depending on the cause of the renal failure.
- b- Extrarenal changes including:
 1. **Fibrinous pericarditis and pleurisy.**
 2. **Uraemic pneumonitis.**

Chapter 7: Diseases of the kidney

3. **Enterocolitis** with ulceration.
4. **Immunodeficiency** with tendency to infections.
5. **Cardiovascular changes of hypertension.**
6. **Renal osteodystrophy** due to secondary hyperparathyroidism.
7. **Normocytic normochromic anaemia** due to decreased erythropoietin production.
8. **Nervous manifestations:** Mental changes, peripheral neuritis and coma.
9. **Fluid, electrolyte and acid-base disturbances.**

Tumours of the kidney

A- Tumours of the kidney tissue:

1. **Benign tumours** such as adenoma, fibroma, lipoma, angiomyolipoma and oncocytoma.
2. **Malignant tumours:**
 - i) Primary:
 - Renal cell carcinoma (Hypernephroma).
 - Embryoma (Wilms' tumour or Nephroblastoma).
 - ii) Secondaries from:
 - Carcinomas of the lung, breast and prostate.
 - Sarcomas, like osteosarcoma.
 - Malignant melanoma and choriocarcinoma.

B- Tumours of the renal pelvis:

1. **Benign** such as villous papilloma, haemangioma and fibroma.
2. **Malignant:**
 - i. Primary carcinoma such as transitional cell carcinoma, sarcoma (rare).
 - ii. Secondary, rare.

1- Benign renal tumours:

Renal adenoma: well defined, encapsulated, dermal

- It is a **benign, small (0.5 cm)** cortical foci of tubular or papillary epithelium.
- Present in 40% of adult kidneys.

Angiomyolipoma: microscopic consist of papillae and tubular lined

A benign neoplasm, **well circumscribed yellow to grey tan, soft in consistency, formed of blood vessels, smooth muscles and adipose tissue.**

Chapter 7: Diseases of the kidney

Oncocytoma

A benign tumour, represents 10% of renal tumours.

Gross: well-circumscribed large, brown mass with a central stellate scar.

Microscopic: formed of eosinophilic epithelial cells with uniform rounded nuclei.

2- Malignant renal tumours:

Renal cell carcinoma (RCC):

- It arises from the epithelial cells of the renal tubules.
- The age of incidence ranges from 60 to 70 years.
- The male to female ratio is 2:1.

Risk factors:

- Smoking and with occupational exposure to cadmium.
- The risk is increased 30-fold in individuals with polycystic disease as a complication of chronic dialysis.

Genetic factors:

1. Clear RCC: most cases are sporadic, but also occurs in familial forms or in association with Von Hippel-Lindau (VHL) disease. VHL disease is an autosomal dominant disease, characterized by hemangioblastomas of the cerebellum and retina and bilateral multiple clear cell carcinomas (in 40% to 60% cases). VHL gene is a suppressor gene.
2. Papillary RCC: occurs in familial and sporadic forms, due to mutation in MET proto-oncogene (a growth factor receptor).
3. Chromophobe RCC: having multiple losses of entire chromosomes.

Gross appearance of renal cell carcinoma:

- Most RCCs are well delineated and centered in the cortex.
- The cut surface is solid, golden-yellow with areas of haemorrhage, necrosis and cystic change (Fig. 7.21).
- Extension to the renal pelvis occurs early and extension to the renal capsule occurs late.

Microscopic:

1- Clear cell renal cell carcinoma (65%)

- It consists of malignant cells arranged in solid masses, or cords but there may be tubules and even dilated cysts with papillary formation.

- The cells are large with clear cytoplasm, resulting from the accumulation of glycogen (clear cell type). *or granular*
- The stroma is scanty and very vascular with areas of haemorrhage and necrosis (Fig. 7.22).

2-Papillary renal cell carcinoma (10-15%):

It consists of branching papillae covered by a single layer of cells with large nuclei and small amount of cytoplasm (Fig. 7.23).

3-Chromophobe renal cell carcinoma (5%):

It consists of large cells with granular eosinophilic cytoplasm prominent cell membranes arranged in a compact pattern (Fig. 7.24).

Spread:

1. Local infiltration of kidney tissues and later infiltration of the renal capsule and perinephric fat.
2. Blood spread: The most common sites of distant metastases are the lungs, bones (particularly the pelvis and femur), central nervous system and suprarenal glands. Blood spread is due to invasion of the renal veins. Left renal vein invasion may lead to varicocele on the left side.
3. Lymphatic spread, to the lumbar group of lymph nodes. *para-aortic, iliac*

Clinical:

Renal cell carcinoma may present by the following:

- a- Haematuria, often painless haematuria.
- b- Flank pain and mass in the region of the kidney in late cases.
- c- Manifestations due to metastasis in lungs and bones.
- d- Anaemia, fever and weight loss.
- e- Hypertension due to renin secretion.
- f- Polycythemia due to the secretion of an erythropoietic stimulating substance. *paraneoplastic*
- g- Hypercalcemia as a result of production of parathormone-like hormone. *out of cells*
- h- Gynaecomastia as a result of gonadotropin and placental lactogen production. *paraneoplastic*

paraneoplastic syndrome - polycythemia, HT, hypercalcemia, gynaecomastia

① paraneoplastic syndrome - polycythemia, HT, hypercalcemia, gynaecomastia

② spread

③ costovertebral pain and swelling

Wilm's tumour (embryoma-nephroblastoma):

- Most cases occur in children between 2-5 years of age.
- The tumour arises from the embryonic precursor cells

Gross:

- Most Wilm's tumours are rapidly growing, destroying the kidney tissues, and infiltrating the renal capsule.
- Infiltration of the renal pelvis or ureter is a rare and late event.
- The cut surface is homogenous and greyish in colour and often exhibits areas of necrosis and haemorrhage (Fig. 7.25a).

Microscopic: Three major components are identified; undifferentiated blastema, mesenchymal tissue and epithelial tissue (Fig. 7.25b).

- The blastematos areas are extremely cellular, composed of small round to oval primitive cells, the cytoplasm is usually very scanty but sometimes it exhibits an oncocytoid appearance.
- The mesenchymal elements have a spindle cell fibroblast-like configuration but may also exhibit differentiation towards various mesenchymal tissues, particularly smooth muscle, skeletal muscle, cartilage or myxomatous tissue.
- The epithelial component is characterized by the formation of anaplastic masses of malignant epithelial cells which may show glandular, tubular or glomerular formation.

Spread:

- Local infiltration; with destruction of the kidney tissue, invasion of the renal capsule, perirenal soft tissue, adrenal glands, bowel, liver or vertebrae.
- Blood spread; the most common sites of distant metastases are lungs, liver and brain.
- Lymphatic spread to the regional lymph nodes are found in 15% of cases.

Clinical: Patients with Wilm's tumour may present by the following:

- a. Large abdominal mass.
- b. Haematuria.
- a. Abdominal pain.
- b. Intestinal obstruction and hypertension.



Fig.7.21; Renal cell carcinoma

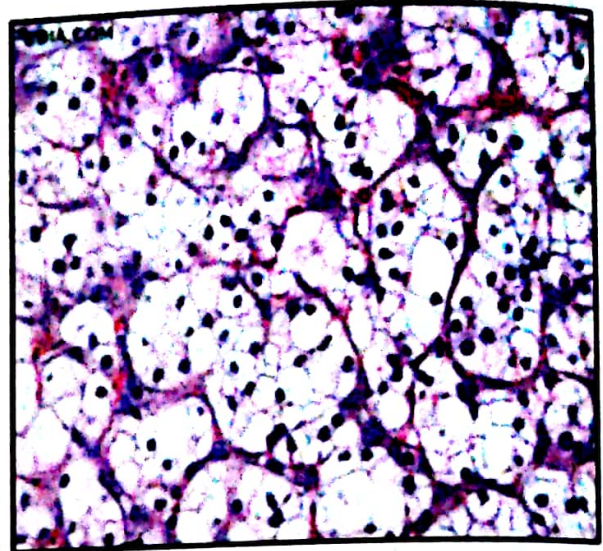


Fig.7.22; Clear type RCC

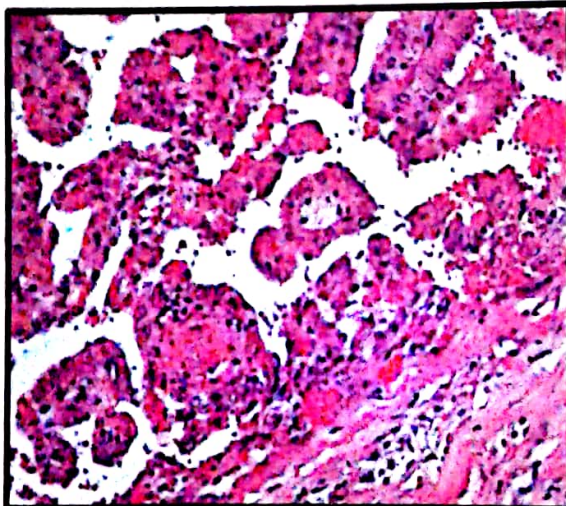


Fig.7.23; Papillary RCC

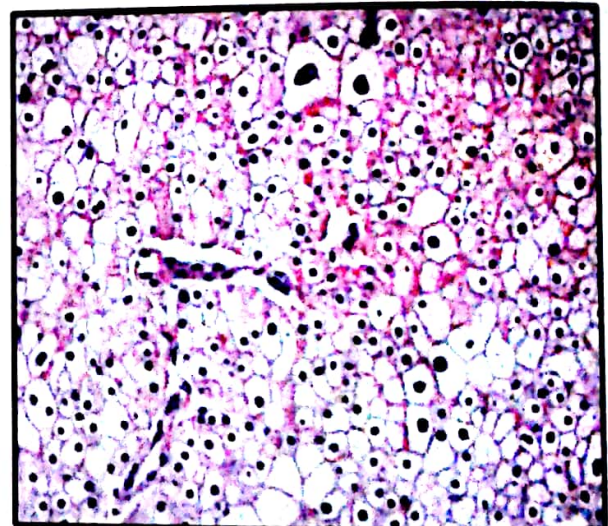


Fig.7.24; Chromophobe RCC

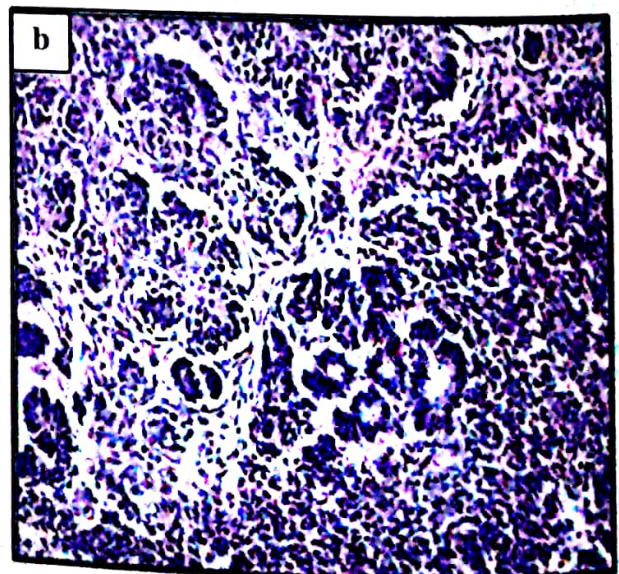


Fig.7.25: Wilm's tumour (a) Gross (b) microscopic

SUMMARY

Congenital anomalies of the kidney and ureters

Renal agenesis, hypoplasia, horse-shoe kidney, aberrant renal artery, adult polycystic kidney disease, childhood polycystic kidney disease.

Pathogenesis of glomerular injury

Antibody-mediated immune injury: Immune complexes or autoantibodies against components of the GBM

Nephrotic syndrome: proteinuria, hypoalbuminemia and edema.

Causes: Minimal change disease, Focal and segmental glomerulosclerosis, Membranous nephropathy. Diabetes, renal amyloidosis & SLE

Nephritic syndrome: hematuria, oliguria with azotemia, proteinuria, and hypertension.

Causes: Acute post-infectious glomerulonephritis IgA nephropathy, hereditary nephritis, rapidly progressive glomerulonephritis

Tubulointerstitial nephritis; Acute and chronic pyelonephritis (obstructive & reflux)

Drug-induced interstitial nephritis

Analgesic nephropathy

Acute tubular necrosis (toxic-anoxic).

Vascular diseases of the kidney; Benign & malignant nephrosclerosis:

Renal stones: Types; Oxalate, urate, phosphate and cystine stones.

Hydronephrosis: It is the dilatation of the pelvis and calyces of the kidney leading to pressure atrophy of the kidney tissue

Tumours of the kidney:

Renal cell carcinoma: clear cell carcinomas, papillary renal cell carcinomas, chromophobe renal cell carcinomas.

Wilm's tumour (embryoma-nephroblastoma).

Tumors of the renal pelvis and collecting system

Villous transitional cell papilloma and transitional cell carcinoma.

Chapter 8

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- 📖 Define cystitis, list types, predisposing factors and describe pathologic features of each type.
- 📖 Classify tumours of the urinary bladder, explain pathogenesis and describe the pathological features of transitional cell carcinoma.
- 📖 Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and / or laboratory findings
- 📖 Enumerate causes of hematuria.
- 📖 Classify tumours of the testis, list risk factors and describe pathological features.
- 📖 Compare and contrast germ and non germ cell tumours of testis.
- 📖 Define prostatitis, list types and describe microscopic features.
- 📖 Identify benign nodular hyperplasia, explain pathogenesis, describe pathologic features and list complications.
- 📖 Describe pathologic features of prostatic carcinoma, explain grading system, spread and methods of diagnosis.

papilla covered by larger than normal or to be > 1 layer (no continuity)
- Central blood vascular
inverted papilloma
- irregular, non-epi, non-typical features, no papillae
- scanty CT

DISEASES OF THE URINARY BLADDER

Congenital anomalies:

1. **Ectopia vesicae (exstrophy):**
 - The anterior wall of the urinary bladder and the overlying part of the anterior abdominal wall are defective, thus exposing the mucosal surface of the posterior vesical wall.
 - It may be associated with epispadias in males and split clitoris in females.
 - It may be complicated by urinary tract infection, squamous or glandular metaplasia of the urothelium, and carcinoma (transitional, squamous, or adenocarcinoma).
2. **Patent urachus:** A fistulous tract that extends from the urinary bladder to the umbilicus, discharging urine to the outside.
3. **Epispadias:** The urethra opens on the dorsum of the penis.
4. **Hypospadias:** The urethra opens on the ventral surface of the penis.
5. **Valves (mucosal folds) in the posterior urethra:** Which may lead to obstruction.

Cystitis:

Cystitis is inflammation of the urinary bladder.

Causative organisms:

- **E. coli** is the commonest type. Other organisms are streptococci, staphylococci, gonococci and bacillus pyocyaneus.
- The organisms reach the urinary bladder from neighboring organs.

Sex: Females are more commonly affected due to short urethra.

Predisposing factors:

The epithelial lining of the urinary bladder is resistant to infection. Cystitis usually occurs due to some predisposing factors as:

1. **Bilharziasis of the urinary bladder** (see general pathology).
2. **Stasis of urine:** due to obstruction in nodular hyperplasia of the prostate, stricture of the urethra and tumours of the urinary bladder.
3. **Inflammation of nearby organs**, such as kidneys, ureters, prostate, vulva, vagina, cervix and urethra.
4. **Trauma** to the urinary bladder by stones or catheter.
5. **General diseases**, such as diabetes.

Types of cystitis:

- (1) Acute cystitis. It is a common disease characterized clinically by frequent micturition, dysuria (burning micturition), pyuria (pus in urine) and suprapubic pain.

Gross: The wall of the bladder is thickened, edematous, red and congested. There may be areas of haemorrhage, ulceration and necrosis.

- (2) Chronic non specific cystitis. It may follow repeated attacks of acute cystitis or may start as such from the beginning.

Gross: In most cases the wall is thickened, congested with increased fibrosis which may lead to granularity of the mucosa and reduction of the lumen of the urinary bladder.

Chronic non-specific cystitis may show one of the following patterns:

- a- Interstitial cystitis: It is a persistent painful form of chronic cystitis occurring most commonly in females. There is non-specific inflammation extending into the muscle layers ending in transverse fibrosis.

- b- Polypoid cystitis: Characterized by polypoid projections of the bladder mucosa due to submucosal edema.

- c- Malakoplakia: This is a rare condition which has been associated with immune deficiency states. The mucosa in the region of trigone shows multiple nodular yellow soft thickenings ranging from 1-4 cm in diameter.

Microscopic: The subepithelial tissues are infiltrated by chronic inflammatory cells with multiple foreign body giant cells containing calcified material known as Michaelis - Gutman bodies which are believed to be an end result of bacterial degradation.

N.B. Various epithelial change may occur in the bladder due to inflammation and irritation as Brunn's nests, cystitis cystica and cystitis glandularis.

- o Leukoplakia: occurs due to squamous metaplasia, often with keratinization and appears as whitish patches.

(3) Chronic specific cystitis:

- a- Bilharzial cystitis: See Part I (General pathology)

- b- Tuberculous cystitis: Infection is usually secondary to renal tuberculosis, but it may complicate TB of the prostate, seminal vesicles, and epididymis in males or fallopian tubes in females. The tubercles are formed in the subepithelial tissue, and the overlying epithelium becomes ulcerated.

Tumours of the urinary bladder

Bernign tumours:

Papilloma, fibroma, leiomyoma, rhabdomyoma, neurofibroma, and angioma.

Malignant tumours:

They are common tumors, **more** frequent **in males** above the age of 40 years. In Egypt, they develop at a younger age due to urinary Bilharziasis.

Risk factors:

- Urinary bladder **bilharziasis**. It may be **due to**:
 - ⊙ **Mechanical irritation** of the ova.
 - ⊙ **Tryptophan metabolites as carcinogenic agents** which are usually present in high concentration in the urine.
 - ⊙ **Metaplastic changes** including **cystitis glandularis** and **squamous metaplasia**.
- Aniline dyes** used by dye workers.
- Cigarette smoking**.
- Chronic irritation** by stones, chronic cystitis.
- Leucoplakia**.
- Congenital anomalies** (ectopia vesicae).

Malignant epithelial neoplasms:

Site: The **region of trigona**, as a consequence, partial or complete blockage of one or both ureters is frequent.

A- Transitional cell carcinoma (TCC):

- Over **90% of bladder cancers** are transitional cell carcinomas.
- **Common in males**.
- Age incidence: between **50 and 80 years**.
- **Precursors of invasive transitional cell carcinoma include: non-invasive papillary urothelial neoplasms and carcinoma in situ.**

Morphology: Urothelial transitional cell neoplasms are classified into:

- Non-invasive papillary urothelial neoplasms;** they **project into the lumen** and **have a delicate papillary appearance** (Fig.8.1,2).

They are graded into:

- **Papilloma** → benign, finger like, not malignant
- **Papillary urothelial neoplasm** of low malignant potential.
- **Low grade papillary urothelial carcinoma** → atypical invasion
- **High grade urothelial carcinoma** → atypical, more invasive

N.B.: **Carcinoma in situ (CIS)** of the bladder is usually **multifocal**, without treatment 50-75% will progress to **muscle-invasive cancer**.

2- Invasive urothelial carcinoma:

It **invades lamina propria** or **extends into the underlying muscle layer**.

It may be:

- **Associated with papillary urothelial cancer** usually of **high grade**.
- **Not associated with papillary growth**, due to **progression of CIS into invasive cancer**.

Gross: **Papillary** or **solid ulcerative lesions** (Fig.8.3a).

Microscopic:

- **High grade infiltrating papillary** or **diffuse sheets of malignant transitional epithelial cells** invading the **lamina propria** or **muscle layer**.
- **Squamous** or **glandular differentiation** commonly occurs.

Prognosis: **The extent of invasion or spread (stage)** at the time of **initial diagnosis** is the most important prognostic factor.

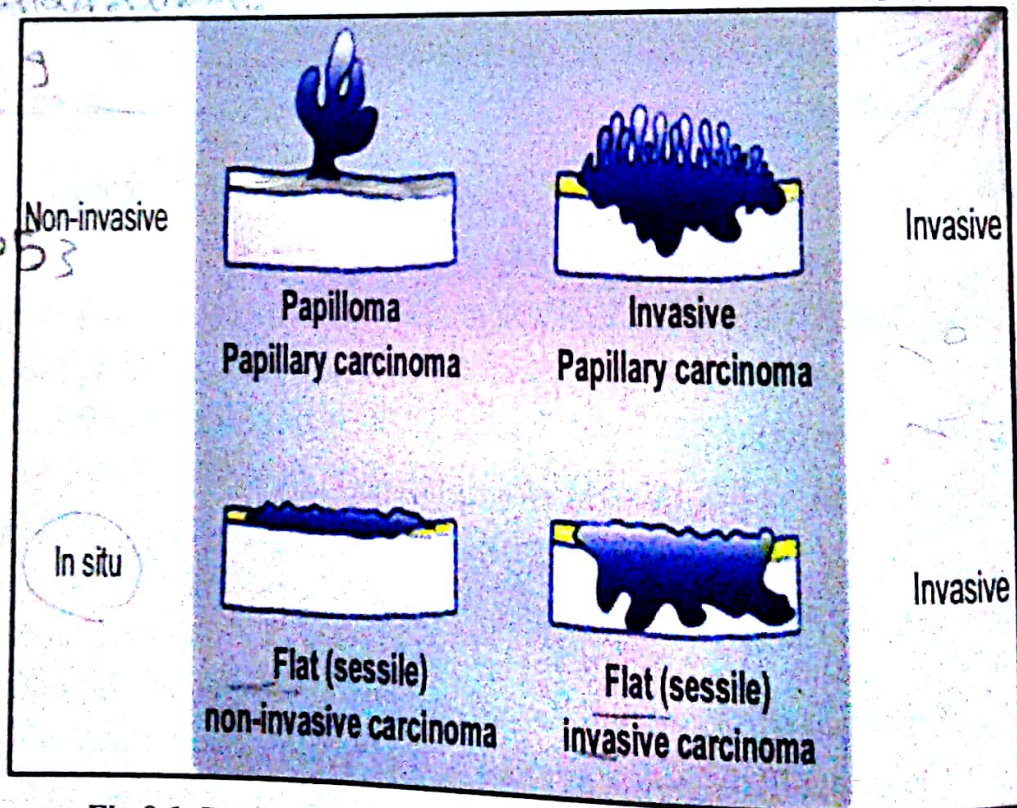


Fig.8.1: Precursor lesions of invasive urothelial carcinoma

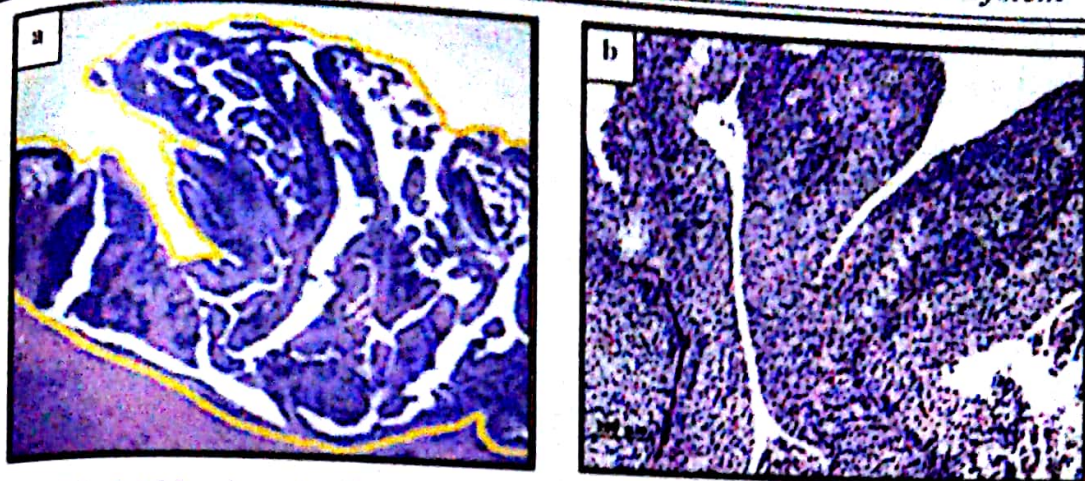


Fig.8.2: Non-invasive low-grade papillary carcinoma (a) Gross (b) Microscopic

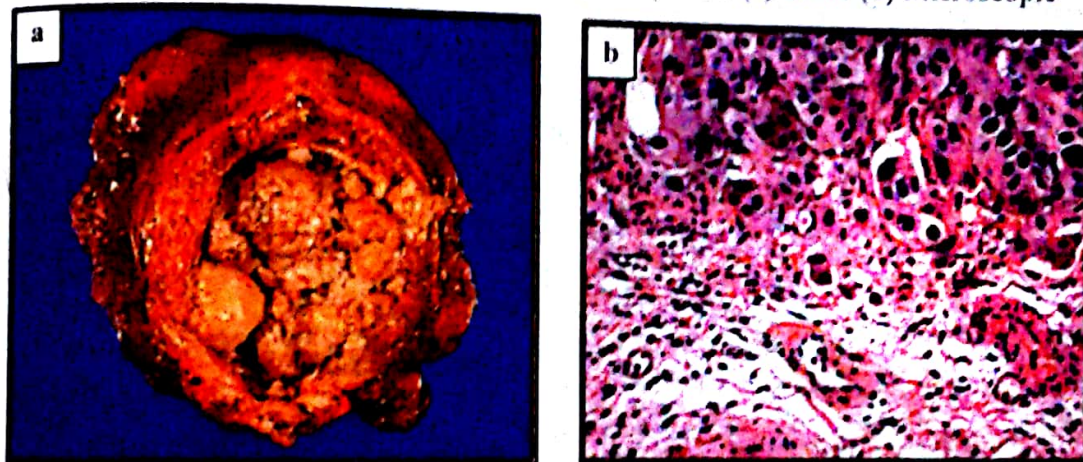


Fig.8.3: Invasive urothelial carcinoma
(a) Fungating infiltrating mass (b) Tumor cells invading lamina propria

B- Squamous cell carcinoma:

- It is common where **bilharziasis** is common (squamous metaplasia).
- **Well differentiated keratinizing squamous cell carcinoma** tends to form a large bulky mass.
- Since **foci of squamous cell** differentiation are common in **high grade transitional carcinoma**, the term squamous cell carcinoma should be reserved for those tumours that are squamous throughout.

C- Adenocarcinoma:

May arise from:

1. **Urachal remnants** in the dome of the bladder.
2. **Areas of cystitis glandularis** (after metaplasia).

Mesenchymal neoplasms:

- **Leiomyoma and leiomyosarcoma.**
- **Embryonal rhabdomyosarcoma** (sarcoma botryoides) in young children.

Hematuria

Definition: It is the presence of blood in urine.

Blood coming from the kidney is usually mixed with urine, **blood** coming from the **urinary bladder** is usually **at the end of micturition** while that coming from the **urethra** is passed **at the beginning of micturition**.

Causes:

1. **Urinary bilharziasis** leading to terminal haematuria.
2. **Inflammatory diseases** such as **post streptococcal glomerulonephritis**, focal embolic glomerulonephritis, cystitis, pyelonephritis and pyonephrosis.
3. **Renal stones**.
4. **Nodular hyperplasia** of the prostate.
5. **Tumours of the urinary system** e.g. villous papilloma, carcinoma of the urinary bladder and renal cell carcinoma.
6. **Circulatory disturbances** such as chronic venous congestion and infarction of the kidney.
7. **Congenital polycystic kidney**.
8. **Haemorrhagic blood diseases** (e.g. purpuras, leukaemias and haemophilia).

Diseases of the male genital system

Congenital defects:

1. Undescended testis (cryptorchidism):

Cryptorchidism is the arrest of one or both testes at any point from the kidney to the scrotum, commonly the inguinal canal.

Complications:

- a- **Testicular atrophy** and **infertility** due to **higher temperature** within the body than in the scrotum.
 - b- A **high risk of malignant testicular tumours**.
2. **Congenital inguinal hernia**, resulting from **persistence of the processus vaginalis** which **connects** the **peritoneal sac** and the **tunica vaginalis** in fetal life.
 3. **Intersexes:** Hermaphroditism, adrenal **virilism**, male pseudohermaphroditism and testicular **feminization**.

Chapter 8: Diseases of the Urinary Bladder and Male Genital System

4. Miscellaneous defects including absence or duplication of testis and absence (atresia) of epididymis or vas deferens.

Inflammatory lesions:

A- Gonorrhoea:

- It is a **suppurative inflammation** of the **anterior urethra** caused by **gonococcus**.
- **Infection** is acquired **through sexual intercourse**.
- Unless treated effectively, the following **complications** may occur:
 1. **Spread of infection to the posterior urethra**, prostate, seminal vesicles, vas deferens and epididymis. Infection in these sites is difficult to eradicate and often becomes chronic with a risk of:
 - a- **Posterior urethral stricture**.
 - b- **Sterility**.
 2. **Ascending infection** to the urinary bladder and kidney leading to **cystitis and pyelonephritis**.
 3. **Haematogenous dissemination** of infection leading to **arthritis**, acute bacterial **endocarditis** and **septicaemia**.

B- Human papilloma virus infection:

- Occurs on the **penis**, caused by **HPV type 6 and 11**.
- Leads to the **formation of condyloma acuminatum**.

C- Tuberculous epididymitis:

Results from **haematogenous spread of tuberculous** infection from a **distant lesion**, usually in the **lungs**.

Complications:

- a- **Chronic sinus discharging caseous material** due to **direct spread** of infection **to the posterior wall of the scrotum**.
- b- **Direct spread** of infection to the **seminal vesicles**, the **base** of the **bladder** and the **testis**.

Orchitis:

It is inflammation of the testis.

The following types are encountered:

1- Acute non suppurative orchitis:

This usually occurs as a **complication of mumps** during postpubertal life. It is characterized microscopically by an **infiltrate of lymphocytes** and **macrophages**. It **usually subsides within few days**, but **residual damage** may lead to **infertility if the condition is bilateral**.

- b- **syphilitic orchitis:**
Occurs in the tertiary stage of syphilis/ the lesion may take the form of gumma or diffuse syphilitic inflammation.

Complications:

- a- **Chronic sinus** usually opening through the **anterior scrotal wall.**
- b- **Fibrosis** of the testis.
- c- **Chronic granulomatous orchitis:**
This usually occurs in **middle age** and probably results from an **autoimmune reaction** to **spermatozoa**/or **germinal epithelium.**
It is characterized microscopically by:
 - a- **Tubular destruction.**
 - b- **Infiltration by lymphocytes, plasma cells, eosinophils and giant cells.**

Tumours of testis

They are composed of germ cell tumors and sex cord/stromal tumors.

Pathogenesis:

The cause of testicular neoplasms remains **unknown/**

Risk factors:

1. **Cryptorchidism**, increases the risk of cancer by 5-10 folds.
2. **Intersex syndromes**, including androgen insensitivity syndrome and gonadal dysgenesis.
3. **Cytogenetic studies** show a wide range of abnormalities in testicular germ cell neoplasms, the most common of which is an **isochromosome of the short arm of chromosome 12/**
4. It is now widely believed that most testicular tumors arise from in situ lesions also called **intratubular germ cell neoplasia.**

Classification and histogenesis:

A- Germ cell tumors: --

- They constitute **95%** of testicular tumors. **All are malignant except mature teratoma occurring in children** ←
 - Germ cell tumors of the testis are divided into two broad categories (**Table.8.1**) based on whether they contain a single histologic pattern (60% of cases) or multiple histologic patterns (40% of cases).
- 1- **Seminomas:** Germ cell tumours arising from primitive cells differentiating along gonadal lines.

3. **Non-seminomatous germ cell tumours:** arising from primitive cells transforming into totipotential cell population giving rise to:

- ❑ **Embryonal carcinoma;** cells remain undifferentiated.
- ❑ **Yolk sac tumour** and **choriocarcinomas;** if they differentiate along extra-embryonic lines.
- ❑ **Teratomas;** if they differentiate along somatic cell lines.

Table 8.1: Simplified Classification of Testicular Germ Cell Tumors

I- Tumors with one histologic pattern (60%)	
Seminoma	Non-seminomatous tumors
- Classical seminoma - Spermatocytic seminoma	- Embryonal carcinoma - Yolk sac tumor - Choriocarcinoma - Teratomas - Mature - Immature - With malignant transformation
II-Tumors with more than one histologic pattern (40%)	

Seminoma:

- This is the commonest malignant tumour of the testis constituting 50% of all testicular germ cell tumours.
- It almost never develops before puberty and has a peak incidence in the forties.

Gross: A well circumscribed soft spherical mass, replacing all or part of the testis. The cut surface is solid, greyish white and homogeneous (Fig.8.4a).

Microscopic:

a- Classical seminoma:

- The tumour is made up of masses of large cells with abundant, pale or clear cytoplasm and large central nuclei, separated by a thin stroma which is usually infiltrated by lymphocytes (Fig.8.4b) and often contains epithelioid granulomas resembling those of sarcoidosis.
- The lymphocytic infiltrate and the granulomas are favourable prognostic features and may represent a defensive immune reaction to the tumour.

b- Spermatocytic seminoma:

- The neoplastic cells resemble secondary spermatocytes. It lacks the lymphocyte infiltrate and granulomas (Fig.8.4c).

- It **never sends metastases** and does not occur in combination with other germ cell tumours. Hence, it has **better prognosis**.
- It occurs at an older age than the classical seminoma.

Prognosis of seminoma:

- **Seminomas are remarkably radiosensitive**.
- About 95% of patients with **spread limited to the para-aortic lymph nodes**.
- It remains localized for a long time and even those cases with lung metastases have a relatively **good prognosis** after radiotherapy.

Embryonal Carcinoma:

This constitutes about 2-3% of all testicular germ cell tumours.

Gross: it differs from seminoma by being **poorly demarcated** and by **presence foci of haemorrhage** and **necrosis in the cut surface**.

Microscopic: it is made up of **large, pleomorphic malignant cells** with an **epithelial appearance arranged in glands, irregular papillae and sheets** (Fig.8.5). The stroma does **not contain lymphocytes or granulomas**.

Prognosis: Embryonal carcinoma is **more aggressive** and **lethal than seminoma**.

Teratoma:

Occurs at any age. **In children, teratomas are typically benign**, while in **post-pubertal males teratomas are malignant**.

Yolk sac (endodermal sinus) tumour:

This occurs in **children less than 3 years** and is **moderately malignant**.

Gross: It is large, **non-encapsulated** and **has a homogeneous, yellow-white, mucinous cut surface**.

Microscopic: It consists of **spaces** and **papillae lined by flattened to cuboidal malignant epithelial cells** containing **eosinophilic hyaline globules positive for alpha fetoprotein (AFP)**. There are **characteristic structures resembling primitive glomeruli, called "Schiller-Duval" bodies** (Fig.8.6).

Choriocarcinoma:

This is a highly malignant tumour made up exclusively of malignant **cyto and syncytiotrophoblasts which produce HCG**.

The tumour **sends early metastases**.

Combined germ cell tumours:

Represents 40% of all testicular germ cell tumours.

Usually consist of a combination of embryonal carcinoma, yolk sac tumor and teratoma.

The prognosis depends on the most malignant element present.

Serum tumor markers in germ cell tumours:

Detection of increased levels of HCG with choriocarcinoma and AFP with yolk sac tumour and teratomas are of value in:

1. Diagnosis.
2. Monitoring response to treatment.
3. Detecting development of metastases.

Table 8.2: Summary of testicular tumours

Tumor	Peak age	Morphology	Tumor markers
Seminoma	40-50	Sheets of uniform polygonal large cells, clear, cytoplasm, round nuclei. Scant stroma with lymphocytes.	10% have elevated hCG
Embryonal carcinoma	20-30	large pleomorphic malignant cells, with large nuclei, arranged in sheets, glands, may contain yolk sac or choriocarcinoma.	Negative (pure embryonal carcinoma)
Yolk sac tumor	3	Schiller Duvall bodies	90% have elevated AFP
Chorio-carcinoma	20-30	Malignant cytotrophoblastic & syncytiotrophoblastic cells	100% have elevated hCG
Teratoma	All ages	Tissue from all 3 germ cell layers, with different grades of differentiation	Negative (pure teratoma)
Mixed tumors	15-30	Commonly, teratoma and embryonal carcinoma	90% have elevated hCG or AFP or both

Peripheral
12.5% teratoma

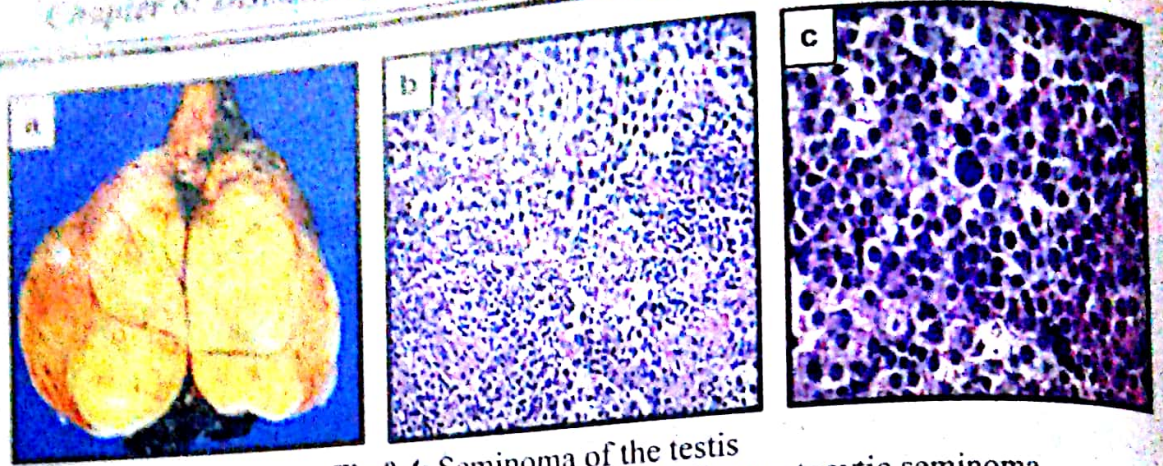


Fig.8.4: Seminoma of the testis
(a) Gross appearance, (b) Classical seminoma (c) Spermatocytic seminoma

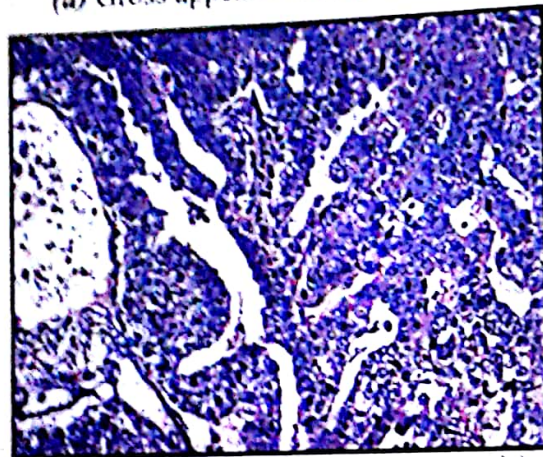


Fig.8.5: Embryonal carcinoma

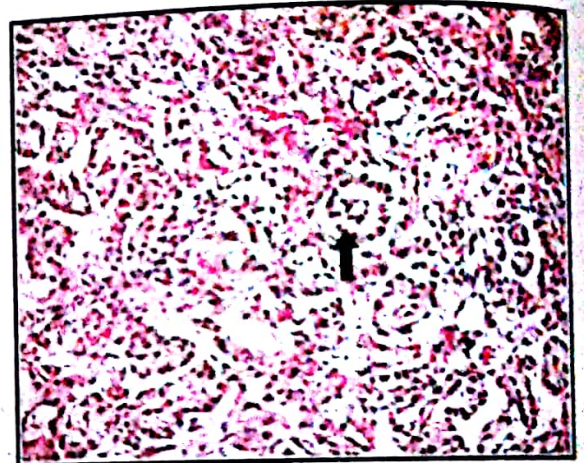


Fig.8.6: Yolk sac tumour, note Schiller-Duval body (arrow)

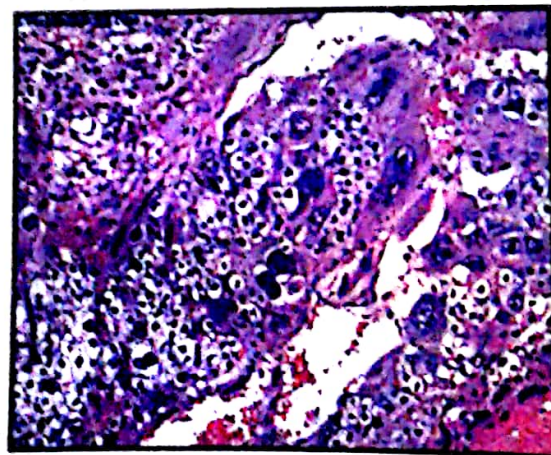


Fig.8.7: Choriocarcinoma

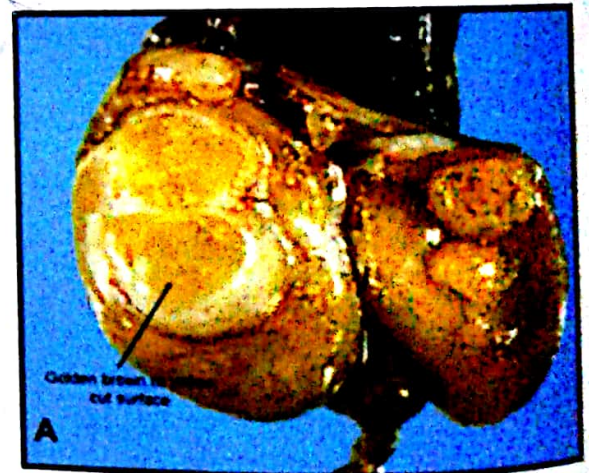


Fig.8.8: Leydig cell tumor

B. Sex cord stromal tumours:

Sertoli and Leydig cell tumours:

- ☐ These are rare
- ☐ The former produces oestrogen, while the latter produces testosterone
- ☐ They are usually benign (Fig.8.8).

C. Other tumours:

1. Testicular Lymphoma (7% of testicular tumours): This usually occurs in **old age**. It is usually a **diffuse large cell lymphoma**.
2. Adenomatoid tumour of the epididymis: A rare, **benign** tumour arising from the **mesothelium of the tunica vaginalis covering the testis**.
3. Soft tissue tumours not specific to the testis: Rare and include leiomyoma, lipoma, liposarcoma and rhabdomyosarcoma, etc...
4. Spread of malignant tumours of the testis:
 - ⊗ **Direct** leading to destruction of testicular tissue and scrotal skin.
 - ⊗ **Lymphatic** to parailiac, paraaortic and inguinal lymph nodes.
 - ⊗ **Blood spread** to lungs and other organs.

Tumours of penis

More than 95% of penile tumours arise from the squamous epithelium.

Predisposing factors: **Poor hygiene, smoking, infection by human papilloma virus type 16 and 18.**

- a. Squamous carcinoma in situ (Bowen's disease): may proceed to invasive carcinoma in 10% of cases.
- b. Invasive squamous carcinoma: appears as **indurated ulcerated mass** and microscopically, it is a typical **keratinizing squamous cell carcinoma**.

Miscellaneous lesions:

1. Hydrocele: Collection of clear fluid within the tunica vaginalis.
Causes:
 - a- Inflammation or tumour of testis.
 - b- Part of generalized oedema.
 - c- Idiopathic.
2. Pyocele: Collection of pus within the tunica vaginalis. It usually follows epididymal infection (gonococcal or nonspecific spreading from urethra or other parts of urinary tract along the vas).
3. Haematocele: Collection of blood within the tunica. It results from trauma or testicular tumours.
4. Varicocele: Varicosity of the pampiniform plexus of veins. It is commonly of unknown cause and is commoner on the left side. It may lead to depression of spermatogenesis with impairment of fertility.
5. Spermatocele: A small cyst filled with fluid containing spermatozoa. It results from obstruction of an epididymal tubule.

Diseases of the prostate

Prostatitis:

Nonspecific prostatitis:

- Acute prostatitis: This is a suppurative inflammation which can be caused by bacteria that cause urinary tract infection, mostly E.coli, less commonly Klebsiella, Proteus, Pseudomonas and Gonococcus. The organisms most commonly reach the prostate by direct extension from the posterior urethra or the urinary bladder.
- Nonspecific chronic prostatitis: May be a sequel of acute prostatitis or appears insidiously. It is caused by the same organisms responsible for acute prostatitis!

Granulomatous prostatitis:

Two forms of granulomatous prostatitis are recognized:

- Nonspecific granulomatous prostatitis, which may follow acute or chronic prostatitis or may have an autoimmune basis.
- Tuberculous prostatitis, which is usually secondary to tuberculosis of the urinary bladder, kidney or less commonly due to haematogenous spread from pulmonary tuberculosis.

Benign nodular hyperplasia

Definition: Excessive androgen-dependent growth of glandular and stromal elements of the central (periurethral) prostatic tissue that occurs in old age.

It is present in most men above the age of 50 years, but is severe enough to cause symptoms (mainly urethral obstruction) in only 5 - 10% of cases.

Pathogenesis of prostatic hyperplasia:

The level of 5 α -reductase enzyme is increased by age. This enzyme converts testosterone into dihydroxy testosterone (DHT) which is more potent than testosterone by 5 times and affects the central zone of the prostate.

Gross:

- The prostate is enlarged and increased in weight (normally, about 14 gr.).
- The enlargement mainly affects the two lateral lobes (i.e. the prostatic tissue on either side of the urethra) as well as the middle lobe (i.e. the prostatic tissue just behind the urethra).
- The enlarged middle lobe forms a rounded mass that projects into the base of the urinary bladder just behind the urethral orifice.
- The affected prostatic tissue is firm and its cut surface is whitish and nodular (Fig.8.9a).
- The cut surface may also show cysts containing milky secretion, infarcts or abscesses.

Microscopies:

- There is an **increase** of both **glandular elements** and **fibro-muscular stroma** of the prostate.
- A **variable number of acini** are **cystically dilated** and there are often **papillary projections** from the gland lining **into the lumen** (Fig. 8.9b).
- Small **concentrically laminated eosinophilic or calcified structures** known as **corpora amylacea** are commonly found in the **gland lumina**.
- **Areas of infarction** may be seen and are usually **surrounded by squamous metaplasia** of the epithelium lining the near-by acini.

Effects and complications:

1. On the urethra:

- a. **Dysuria** due to compression of the urethra by the enlarged prostate leads to difficulty of micturition.
- b. **Hematuria**; due to congestion of the urethral mucosa.
- c. **Acute urinary retention** due to urethral obstruction.

2. On the urinary bladder:

- a- **Dilatation and hypertrophy** of the bladder with trabeculation of its mucosal surface consequent to obstruction to the outflow of urine.
- b- **Residual urine due to accumulation** in the pouch (diverticulum) formed behind the enlarged middle lobe.
- c- **Incontinence of urine due to stretching** of the urethral sphincter by the enlarged middle lobe.
- d- **Cystitis and stone formation** predisposed to by accumulation of urine in the urinary bladder.

3. On the ureters and kidneys:

- a- **Bilateral hydroureter** and **hydronephrosis** due to urinary obstruction.
- b- **Ascending infection** from the bladder leading to pyelonephritis or pyonephrosis.
- c- **Renal failure due to** hydronephrosis (Fig. 8.10).

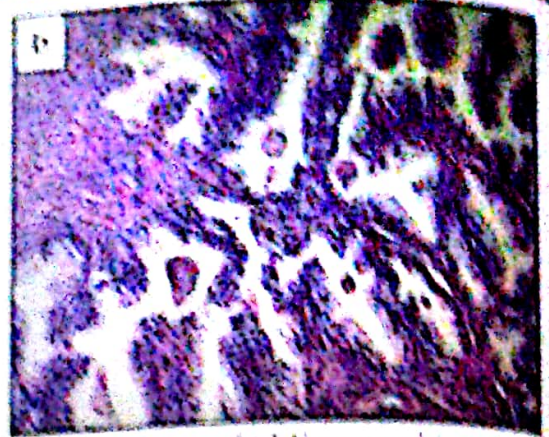
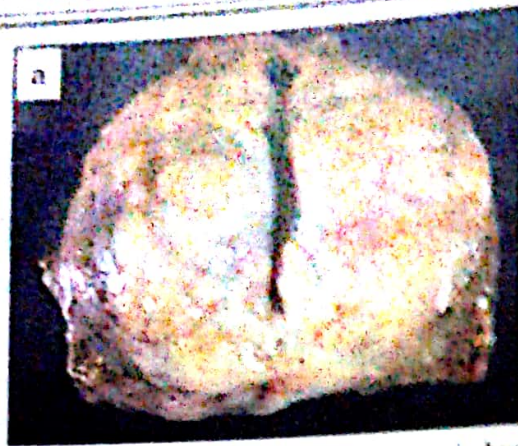


Fig.8.9: Benign prostatic hyperplasia (a) Gross, (b) Microscopic

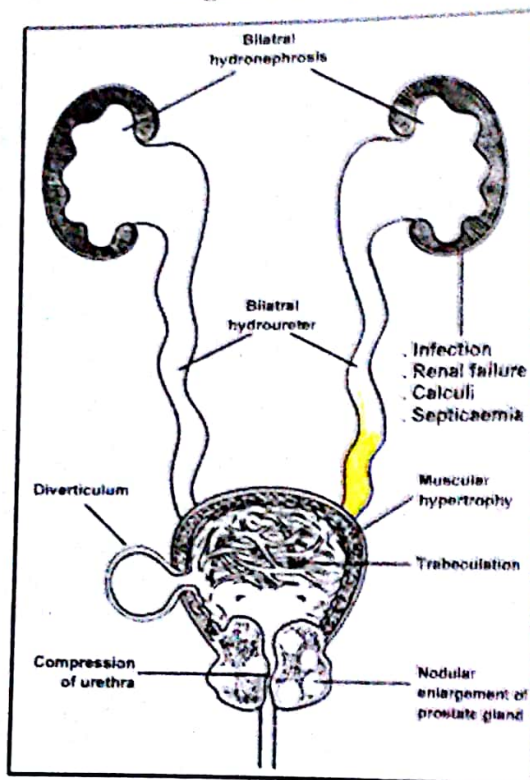


Fig.8.10: Complications of prostatic hyperplasia.

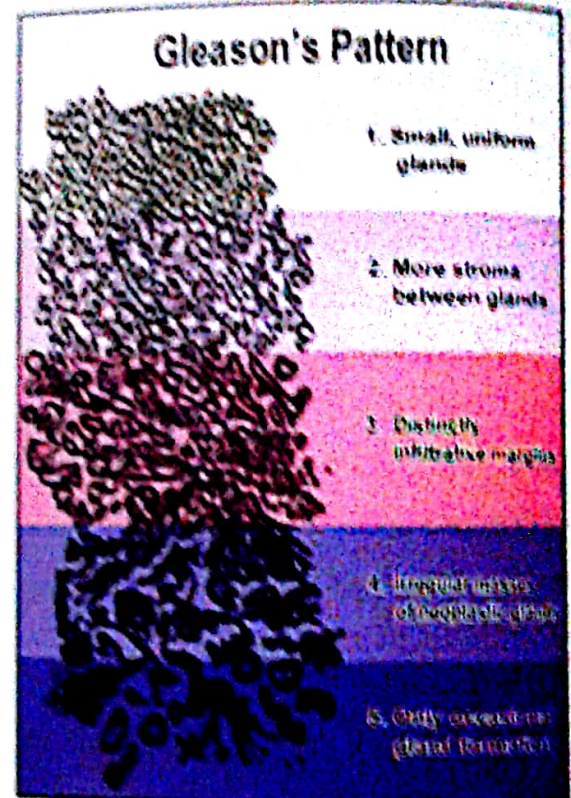


Fig.8.11: Gleason system of grading prostate cancer.

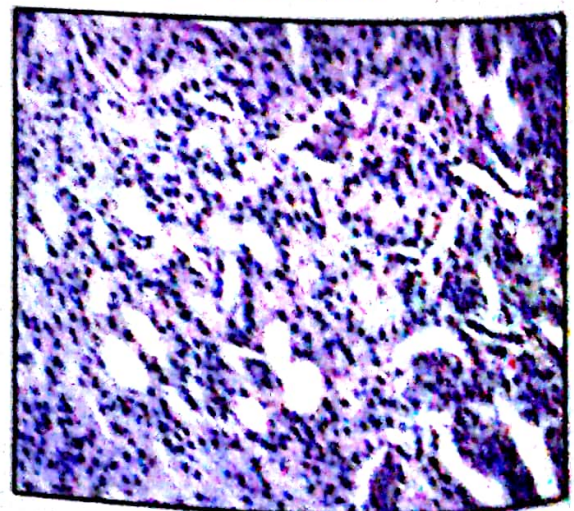
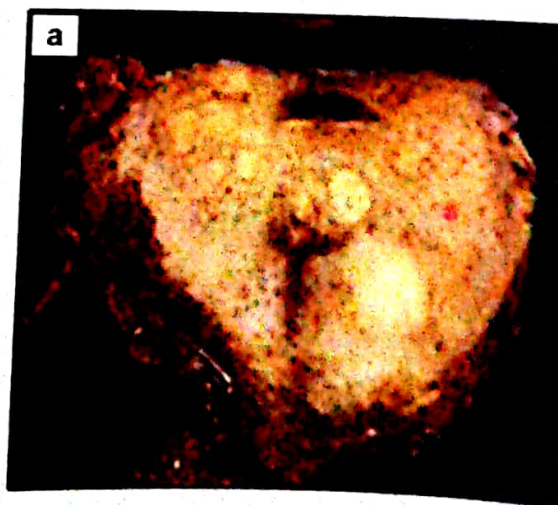


Fig.8.12: Carcinoma of the prostate (a) Gross, (b) Microscopic.

Carcinoma of the prostate:

This is one of the commonest cancers in males.
It occurs mainly in old men above the age of 50 years.

Gross:

- The tumour frequently arises in the **periphery of the gland especially posteriorly**, but may arise anywhere in the prostate.
- It forms a **firm, ill-defined mass** with a **gray-white cut surface** (Fig.8.11a).

Microscopic:

adenocarcinoma

1. Most prostatic adenocarcinomas are **moderately differentiated** and **consist of small, closely packed acini**, each **lined by a single row of uniform cells** showing **prominent nucleoli**. **Mitotic figures are rare** (Fig.8.11b).
2. **Less differentiated cancers** show **large, irregularly spaced acini**, or **cribriform or papillary patterns**.
3. A minority of prostatic cancers are **poorly differentiated**, consisting of **solid sheets or clusters of malignant cells**.

Histologic grading:

- o **The Gleason system**, which is **based on the glandular pattern of the tumour** as noted on low power examination. **Five grades** are recognized, with grade **1** being the most differentiated and **5** being the least differentiated (Fig.8.12).
- o **A three-grade system**; **corresponding to tumours that are well differentiated** (grade 1), **moderately differentiated** (grade 2) and **poorly differentiated** (grade 3).

Spread:

1. **Direct**; towards the **urethra (urethral obstruction)** and to the surrounding tissues mainly the seminal vesicles and the urinary bladder.
2. **Lymphatic**; to **iliac and para-aortic lymph nodes**.
3. **Perineural invasion**; producing **severe pain**.
4. **Blood spread**; to various organs, and to the spine along the paravertebral system of veins; Bone metastases are usually osteoblastic, i.e. stimulate bone formation.

Prognosis:

- Depends on the stage.
- Good for cancers removed while still confined to the prostate.

Prostate cancer
Growth of the prostate cancer is dependent on androgen and therefore androgen and oestrogen administration are commonly adopted in treatment.

Diagnosis of prostate cancer:

1. Rectal examination: The posterior location of most prostatic cancers renders them easily palpable by rectal examination.
2. Transrectal needle biopsy of suspicious areas in the prostate.
3. Cytologic examination of prostatic secretion for malignant cells.
4. Prostate tissue-specific antigen (PSA): High serum levels of PSA are often noted in patients with prostatic cancer. Evaluating PSA concentrations is of great value in monitoring recurrence after treatment.
5. Phosphatases:
 - High serum levels of prostatic acid phosphatase are detected when the tumour has spread beyond the prostate.
 - Elevated serum levels of both acid and alkaline phosphatases occur when the prostatic cancer has metastasized to bone.

(1A)

SUMMARY

Diseases of the urinary bladder:

Cystitis: Acute & Chronic non specific cystitis.

Chronic specific cystitis: Bilharzial & Tuberculous cystitis

Tumours of the urinary bladder:

A- Transitional cell carcinoma (TCC):

1- Non-invasive papillary urothelial neoplasms; they are graded into; Papilloma, papillary urothelial neoplasm of low malignant potential. low grade papillary urothelial carcinoma & high grade urothelial carcinoma.

2- Invasive urothelial cancer:

B- Squamous cell carcinoma: In bilharziasis (squamous metaplasia).

C- Adenocarcinoma: Arise from; urachal remnants or cystitis glandularis.

D- Mesenchymal neoplasms; Embryonal rhabdomyosarcoma, etc.....

Hematuria; causes

Diseases of the male genital system:

Cryptorchidism: Refers to incomplete descent of the testis from the abdomen to the scrotum. It is associated with tubular atrophy and sterility.

Testicular Tumors

- They occur in undescended testis and in males with gonadal dysgenesis.

Classification:

1- Germ cells are the source of 95% of testicular tumors. Germ cell tumors with single histologic patterns are seminoma, embryonal carcinoma, yolk sac tumors, choriocarcinoma, and teratoma.

Mixed germ cell tumors contain more than one element, most commonly embryonal carcinoma, teratoma, and yolk sac tumors.

2- Sertoli or Leydig cells.

Other tumours: Testicular Lymphoma, adenomatoid tumour of epididymis.

Diseases of the prostate;

Prostatitis: Nonspecific & granulomatous prostatitis.

Benign nodular hyperplasia. Excessive androgen-dependent growth of glandular and stromal elements of the central prostatic tissue in old age.

Pathogenesis of BPH: Increased level of 5 α -reductase enzyme is by age.

Effects and complications: Effects of urethra, bladder, ureters and Kidneys.

Carcinoma of the prostate. This is one of the commonest cancers in males. above the age of 50 years.

Most prostatic adenocarcinomas are moderately differentiated

Histologic Grading:

1- The Gleason system (1-5).

2- A three-grade system; grade 1- 3.

Chapter 9

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- 1. Define non-neoplastic disorders of the vulva; describe their pathologic features, list risk factors and complications.
- 2. Compare between Paget disease of the vulva and that of the breast.
- 3. Identify cervical intraepithelial neoplasia, list risk factors, and describe pathological features and methods of diagnosis.
- 4. Describe the pathological and clinical features of invasive cervical carcinoma.
- 5. Define endometriosis, explain its pathogenesis and describe the pathologic features and list its complications.
- 6. Describe the pathological features of endometrial hyperplasia.
- 7. Classify tumours of the body of the uterus.
- 8. Analyze endometrial carcinoma and diagnose a pathologic condition based on a given clinical and radiologic data.
- 9. Define and classify mesenchymal tumours of the uterus and list causes of uterine bleeding in post menopausal females.
- 10. Compare and contrast between complete and partial mole.
- 11. Describe the pathologic features of different types of salpingitis.
- 12. Describe the pathologic features of non neoplastic ovarian cysts.
- 13. Classify tumours of the ovary, list risk factors and clinical features.
- 14. Classify surface epithelial tumours of the ovary and compare between serous and mucinous tumours.
- 15. Define functioning ovarian tumours, describe pathological features and clinical manifestations.
- 16. Define and classify ovarian teratoma.
- 17. Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.

DISEASES OF THE FEMALE GENITAL TRACT IDNEY

Diseases of the vulva

Vulvitis: (inflammation of the vulva)

A- Nonspecific inflammation and dermatologic disorders, cause intense itching (pruritus) with subsequent scratching.

B- Specific infection (sexually transmitted).

- 1) **Candidal vulvitis.**
- 2) **Herpes genitalis** (herpes simplex virus "HSV 1 or 2"), causing a vesicular eruption.
- 3) **Gonococcal suppurative infection** of the vulvo-vaginal glands.
- 4) **Syphilis;** primary chancre at the site of inoculation.
- 5) **Human papilloma virus (HPV),** producing condylomata acuminata and vulvar intraepithelial neoplasia.

Non neoplastic epithelial disorders (Dystrophies)

a- Lichen sclerosus; is characterized by atrophic epithelium, usually with dermal fibrosis. It carries an increased risk of developing squamous cell carcinoma (*Fig.9.1*).

b- Lichen simplex chronicus; is characterized by thickened epithelium, usually with an inflammatory infiltrate (*Fig.9.2*).

Both may coexist in different areas in the same person, and both may appear Clinically as white lesions, referred to as *leukoplakia*.

NB: Leukoplakia is a descriptive clinical term for thickened white patches of the mucous membranes.

Tissue biopsy is usually indicated to rule out other causes of white patches and the presence of any epithelial dysplasia.

Bartholin cyst

- Caused by obstruction of the excretory ducts of the glands.
- Gonorrhea and other infections may cause the inflammatory obstruction and produce abscess that must be drained.
- Uninflamed cysts are lined by transitional or flattened epithelium.

Condylomas.

Condylomas are anogenital warty lesions:

a- Condylomata lata.

- Occur in secondary stage syphilis, and are not commonly seen now.
- They are flat, moist, minimally elevated lesions.

b- Condylomata acuminata.

- They are sexually transmitted lesions, occurring on the vulva, perineum, vagina and rarely on the cervix.
- They are caused by human papilloma virus (HPV).
- Vulvar condylomas are not precancerous but may coexist with foci of intraepithelial neoplasia in the vulva (VIN grade I) and cervix.
- VIN I and condylomas are caused by **low risk strains HPV type 6 and 11.**

Gross: Multiple, may be papillary elevated or flat and red pink in colour.

Microscopic: Consists of a tree like proliferation of stratified squamous epithelium with a peculiar perinuclear cytoplasmic vacuolization and nuclear atypia called **koilocytosis**, attributed to the viral effect (**Fig. 9.3**).

Vulvar intraepithelial neoplasia (VIN):

Gross: Multicentric mucosal raised lesions.

Microscopic:

- It is graded into: mild dysplasia (VIN I), moderate dysplasia (VIN II) and severe dysplasia (VIN III) or carcinoma in situ.
- **HPV type 16** is present in 80 - 90 % of cases of high grade VIN (II & III).
- Untreated cases may progress to invasive carcinoma.

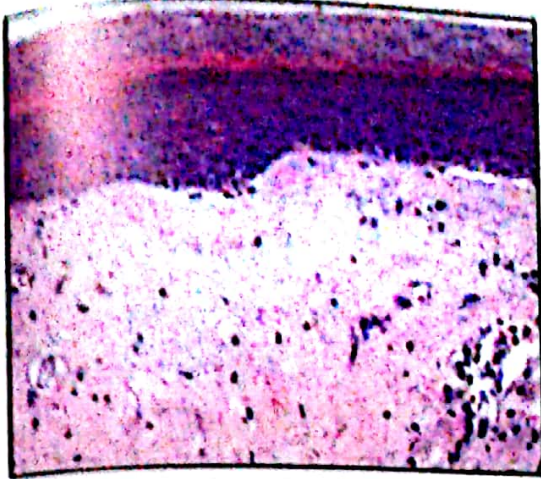


Fig.9.1: Lichen sclerosus.



Fig.9.2: Lichen simplex chronicus.

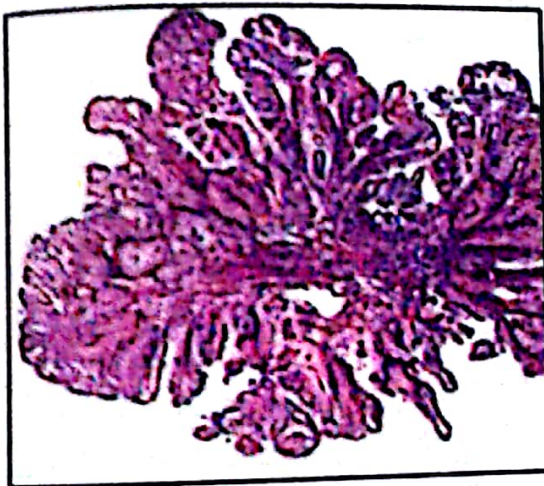


Fig.9.3: Chondyloma acuminata.

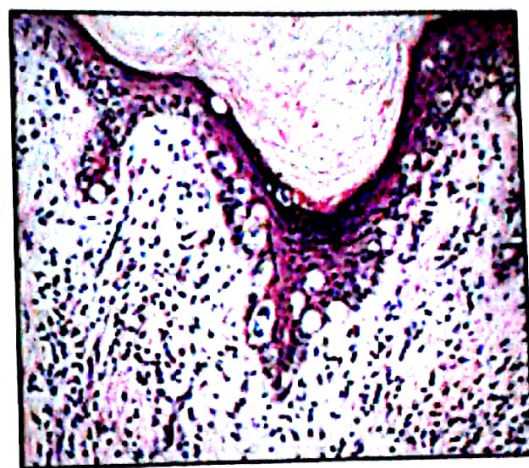


Fig.9.4: Paget disease of the vulva.

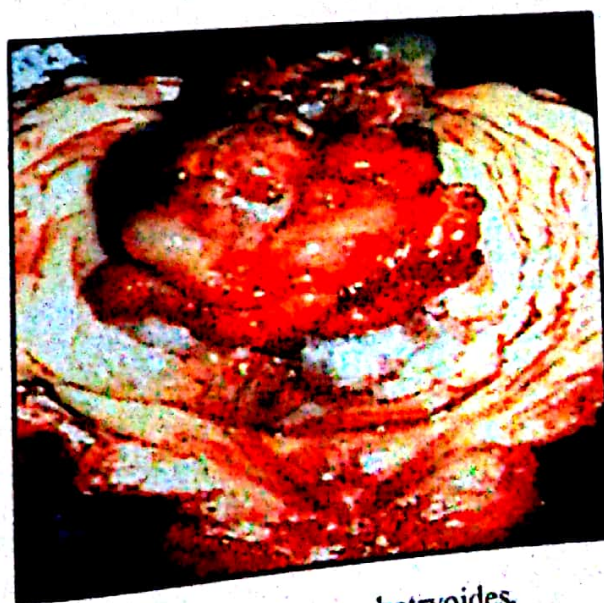


Fig.9.5: Sarcoma botryoides.

Carcinoma of the Vulva:

- ❑ It represents about 3% of all genital tract cancers in women.
- ❑ Occurring mostly in women older than 60 years.
- ❑ Approximately 90% of carcinomas are **squamous cell carcinoma**; the remainder are adenocarcinoma, melanoma, or basal cell carcinoma.

Squamous cell carcinoma of the vulva

There are two distinct forms:

1- HPV-related cases. (high risk strains HPV type 16,18).as in:

- Middle aged women.
- Cigarettes smoking and immunodeficiency.
- Usually proceeded by vulvar intraepithelial neoplasia (VIN).
- Usually poorly differentiated lesions.

2- Non-HPV-related vulvar squamous cell carcinoma; occurs in

- Older individuals.
- Usually well differentiated.
- Associated with lichen sclerosus or other inflammatory conditions.

Paget disease of the vulva (Extramammary Paget disease)

Gross: Red crusted sharply demarcated areas mostly on labia majora.

Microscopic: Characterized by large epithelioid, vacuolated cells present singly or in clusters within the epidermis (**Fig.9.4**).

NB: Unlike Paget's disease of the breast where 100% of cases have an underlying or adjacent ductal carcinoma, vulvar lesions are mostly confined to the epidermis. It may persist for many years without invasion but occasional untreated cases eventually become invasive.

Diseases of the vagina

Congenital anomalies: are uncommon and include:

- 1- **Atrophy or total absence** of the vagina and uterus.
- 2- **Septate or double vagina** (usually associated with a septate cervix and, sometimes, uterus).
- 3- **Gartner duct cyst** arising from persistent embryonic remnants of the wolffian (mesonephric) duct, seen on the **lateral vaginal wall**.

Vaginitis:

It is relatively common; it produces vaginal discharge (leukorrhea).

a- **Normal commensals (Doderline bacilli, lactobacillus)** that become pathogenic in conditions such as diabetes, systemic antibiotic therapy, after abortion or pregnancy, or in elderly persons and in patients with the acquired immunodeficiency syndrome.

b- **Monilial vaginitis:**

- Caused by *Candida albicans*.
- It produces a curdy white discharge.
- Common in diabetics, with prolonged antibiotic therapy or sexual infection of a new more aggressive strain.

c- **Trichomonal vaginitis:**

- It is a common disease caused by a flagellate organism (*Trichomonas vaginalis*).
- It produces a watery, copious gray-green discharge

Vaginal Intraepithelial Neoplasia:

- Extremely uncommon, occur in women older than age 60 years.
- It is associated with HPV infection in nearly all cases.

Tumours of the vagina:

A- **Benign tumours;** are rare e.g., Leiomyoma, neurofibromas, etc...

B- **Malignant tumours:-**

1- **Sarcoma botryoides:**

- It is a rare malignant tumour mostly occurring in young girls.
- It arises from the upper vagina and appears as a reddish soft papillary mass filling the vagina (Fig. 9.5).
- **Microscopic;** it is a *rhabdomyosarcoma* with myxomatous areas.

2- **Clear cell adenocarcinoma,** very rare tumour, occurring in young women whose mothers took diethylstilbestrol (DES) during pregnancy.

3- **Squamous cell carcinoma (SCC);** very rare

Pelvic inflammatory disease: (P.I.D.):

It refers to an ascending infection that begins in the vulva or vaginal glands. It usually spreads upwards to involve entire genital tract.

Causes:

- Gonococcus, is the most common causative organism.
- Postpartum and postabortal PID, usually caused by staphylococci, streptococci or coliform bacteria.
- Chlamydial infection.

Complications:

1. Salpingitis: May lead to salpingo-oophoritis, pyosalpinx and tubo-ovarian abscess. Untreated cases may lead to infertility if bilateral.
2. Acute suppurative peritonitis, whether localized or generalized. Fibrous adhesions and blockage of oviducts may occur.
3. Blood spread leading to bacteremia, septicaemia and systemic pyaemia.
4. Intestinal obstruction: due to adhesions between the small bowel and pelvic organs.

Diseases of the cervix

Development of the cervical transformation zone:

- During development, the columnar mucus-secreting epithelium of the endocervix meets the squamous epithelial covering of the exocervix at the external os.
- With the onset of puberty, the squamo-columnar junction undergoes eversion, causing the columnar epithelium to become visible on the exocervix and may appear reddened and moist (*erosion*).
- The exposed columnar cells, however eventually undergo squamous metaplasia, forming a region called the transformation zone (**Fig.9.6**).

Cervicitis:

- Cervicitis refers to inflammation of the cervix.
 - It is extremely common, caused by chlamydia trachomatis (40% of cases), trichomonas vaginalis, candida, neisseria gonorrhoeae, herpesvirus 2 (HSV-2) and HPV, all of which are sexually transmitted.
- 1- **Acute nonspecific:** It is relatively uncommon being limited to postpartum women, caused by staphylococci or streptococci.
 - 2- **Chronic cervicitis:** Common in all women of reproductive age.

Gross:

- In mild and early cases the cervix may appear normal or appear red, swollen and granular.

- In severe chronic cases the cervix may show nabothian cysts (due to blocking the orifices of endocervical glands).

Microscopic:

- There is infiltration by many inflammatory cells and nabothian cysts.
- The mucosa may show squamous metaplasia with or without reactive atypia.

Condyloma of the cervix:

It is caused by HPV, the lesions may be:

- **Flat condyloma** (90% of cases), the epithelium is hyperplastic with koilocytotic atypia in the upper and middle layers.

Mild atypia is associated with HPV 6 and 11 while high grade atypia is associated with HPV 16, 18.

Condylomma acuminatum: as that of the vagina.

Endocervical polyp:

It is an inflammatory non-neoplastic polypoid mass protruding from the endocervical mucosa into the ectocervix or even the vagina.

It is a common lesion, occurs in 2-5% of adult women.

Pathogenesis; inflammation, trauma and pregnancy have been implicated.

Gross; They vary from small and sessile to large soft masses.

Microscopic: They are made up of connective tissue stroma containing dilated mucous secreting glands and covered by columnar epithelium that may show squamous metaplasia.

Clinical: It causes post coital bleeding or vaginal discharge.

Cervical neoplasia

(Cervical intraepithelial neoplasia and invasive carcinoma)

Most tumours of the cervix are epithelial in origin and are caused by oncogenic strains (16, 18) of HPV.

Pathogenesis of cervical neoplasia:

- HPV, the causative agent of cervical neoplasia has a tropism for the immature epithelium of the transformation zone.
- HPV is detected in nearly all cases of cervical intraepithelial neoplasia (CIN) and cervical carcinoma.

• The main risk factors for developing CIN and invasive carcinoma are:

- 1. Early age of onset of sexual intercourse.
- 2. Multiple high risk sexual partners.
- 3. Persistent infection with high risk strains of human papilloma virus.

NOTE:

- HPV type 16, 18 are being implicated as promoter of cervical carcinoma.
 - HPV types 16, 18 usually integrate into the host genome and express large amounts of E6 and E7 proteins, which inactivate tumor suppressor genes p53 and RB, respectively.
 - The affected cells become transformed, capable of autonomous growth and the acquisition of further mutations.
- Cofactors, smoking, immunodeficiency and other gene mutations help in progression of CIN into invasive cancer.

NB: The recently introduced HPV vaccine is very effective in preventing HPV infections and hence cervical cancers.

Cervical intraepithelial neoplasia:

- It is HPV related precancerous epithelial change.
- Usually precedes the development of invasive cancer by many years.
- The peak age incidence is between 30 and 40 years.

Microscopic:

- CIN is characterized by abnormal cellular proliferation, loss of maturation and cytological atypia.

Classification of CIN:

1. **CIN I (Mild dysplasia):** the dysplastic changes occupy the lower 1/3 of the epithelium and koilocytotic changes in the superficial layers of the epithelium (Fig. 9.8b).
2. **CIN II (Moderate dysplasia):** dysplasia extends into the middle third of the epithelium. It takes the form of delayed maturation of keratinocytes some variation in cell and nuclear size. The superficial layer shows some differentiation, and may show koilocytotic changes (Fig. 9.8c).

3. **CIN III (Severe dysplasia)**; there is complete loss of maturation, greater variation in cell and nuclear size, marked chromatin heterogeneity, disordered orientation of the cells, and normal or abnormal mitoses; these changes affect **all layers of the epithelium**. koilocytotic changes are usually absent (**Fig. 9.8d**).

Progression of CIN

For simplification; recently CIN I is renamed **low-grade squamous intraepithelial lesion (LSIL)** and CIN II and CIN III combined into one category referred to as **high-grade squamous intraepithelial lesion (HSIL)**.

Lesion	Regress	Persist	Progress
LSIL (CIN I)	60%	30%	10% (to HSIL)
HSIL (CIN II & III)	30%	60%	10% (to carcinoma)

Diagnosis

CIN produces no alterations recognizable to the naked eye so the diagnosis depends on:

1. **Exfoliative cytology**: using Pap smear to detect the characteristic neoplastic cells. Pap smear remains the **most successful cancer screening test** ever developed (**Fig. 9.9**).
2. HPV can be detected and typed by molecular methods.
3. **Colposcopy**: Ascope to visualize the cervix using:
 - a- **Schiller's test**: involves painting the cervix with a solution of lugol's iodine. The normal cervix rich in glycogen stains mahogany brown. The neoplastic foci being depleted of glycogen fail to stain.
NB: Inflammatory areas also fail to stain.
 - b- **Painting the cervix with 5% acetic acid**, areas of white epithelium (**aceto-white areas**) with abnormal vascular patterns referred to **mosaic** or **punctuation** are diagnostic of cervical neoplasia.
4. **Biopsy** from suspicious areas using:
 - Punch biopsy.
 - Scraping using endocervical special curette.

Invasive cervical carcinoma:

The most common cervical carcinomas are:

- Squamous cell carcinomas (75%)
- Adenocarcinomas and adenosquamous carcinomas (20%)
- Small-cell neuroendocrine carcinomas (<5%).

Squamous cell carcinomas

- Peak age incidence is 45 years, 10 to 15 years after detection of CIN.

Gross: The tumour develops in the transformation zone. It is usually friable and bleeds on touch, and appears as;

- Fungating mass projecting into the vagina (**Fig.9.10**).
- Ulcerative type.
- Infiltrative type.

Microscopic: Conventional squamous cell carcinoma (Grade 1-4).

Spread:

1. Local: to the vagina, urinary bladder, rectum, uterus and broad ligaments.
2. Lymphatics: to regional lymph nodes i.e., iliac, sacral and hypogastric.
3. Blood borne spread: occurs late and in advanced cases.

Clinical features and Effects:

1. Patients present with abnormal vaginal bleeding usually post coital leukorrhea, painful coitus (dyspareunia) and dysuria.
2. Malignant fistula: e.g. vesicovaginal and rectovaginal in advanced cases.
3. Pyometria i.e. accumulation of pus in the uterine cavity due to obstruction of cervical canal followed by infection.
4. Uraemia: due to infiltration of both ureters and is a common cause of death.

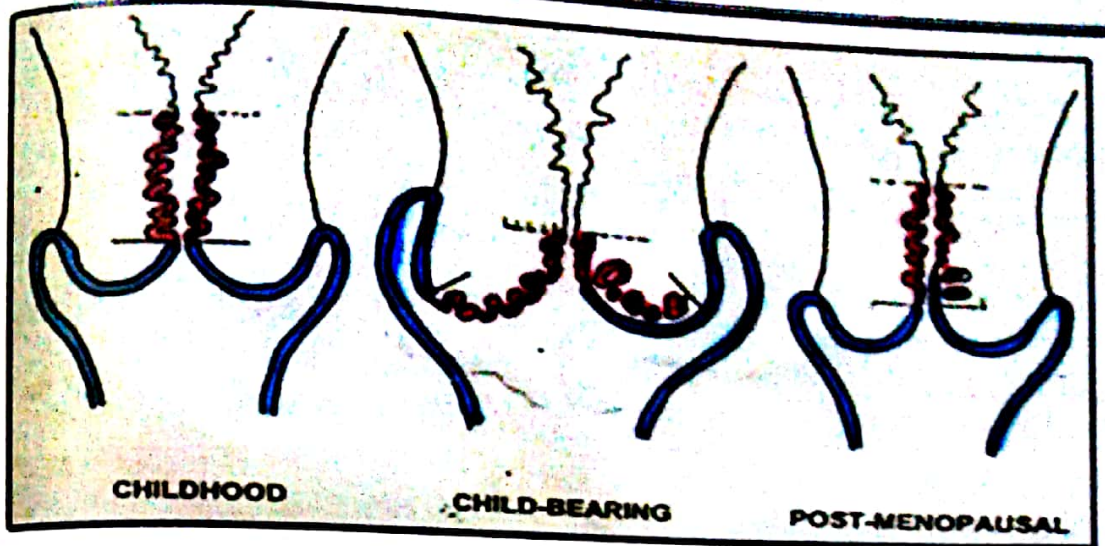


Fig.9.6: Transformation zone

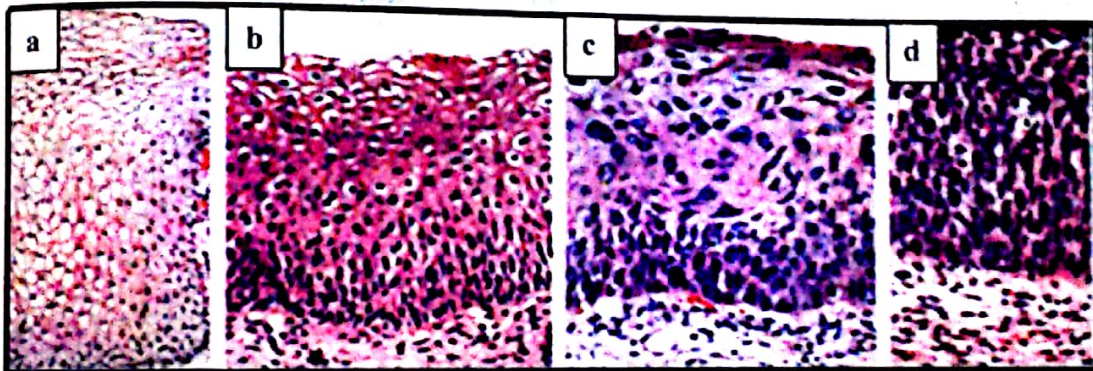


Fig.9.8: a) normal b) CIN I c) CIN II d) CIN III

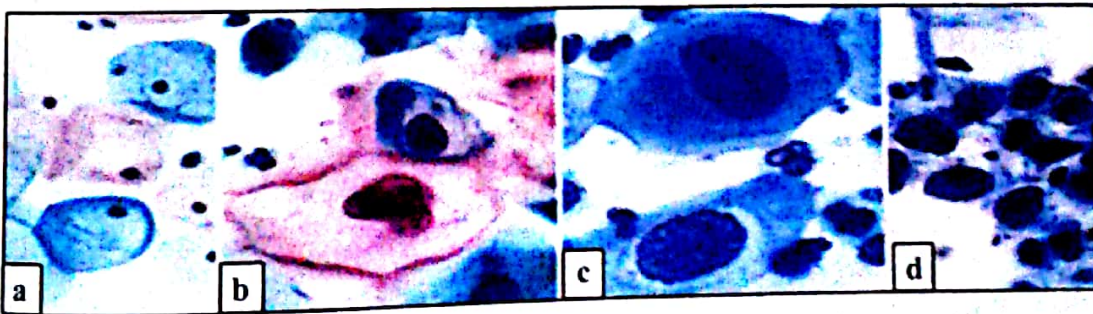


Fig.9.9: a) Normal b) CIN I c) CIN II d) CIN III

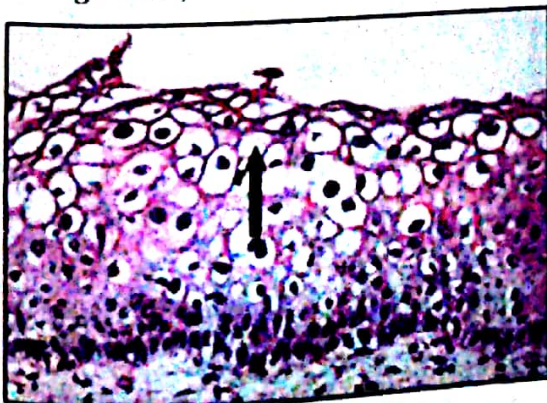


Fig.9.7: Flat condyloma, CIN I with koilocytosis (arrow)

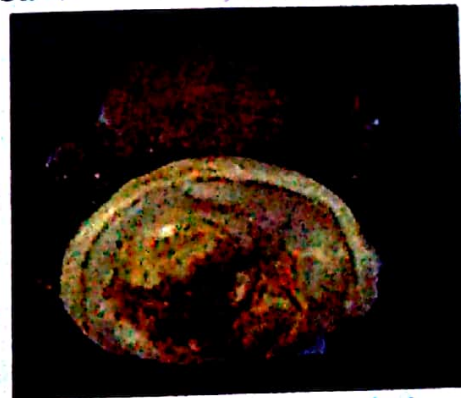


Fig.9.10: Fungating cervical squamous cell carcinoma

Diseases of the body of the uterus

Endometritis:

It is inflammation of the endometrium.

A- Acute endometritis:

- Acute suppurative endometritis is the most common genital tract infection following delivery (puerperal sepsis) or abortion.
- It is caused by many pathogens: group A streptococcus, staphylococcus aureus, C. trachomatis, N. gonorrhoeae, E. coli, that contaminate instruments or from the attendants.

Gross: The uterus is enlarged and soft.

Microscopic:

- In mild cases the endometrium is oedematous, congested and infiltrated by numerous neutrophils and pus cells.
- In severe cases the endometrium is necrotic and the acute inflammatory cells spread to infiltrate the myometrium as well.

Clinical: Abdominal pain, fever, and purulent vaginal discharge.

Complications: As in pelvic inflammatory disease.

B- Chronic endometritis:

1- Chronic non-specific endometritis.

a- Postabortive endometritis:

- It follows abortion and is usually accompanied by retention of some products of conception.

b- Senile endometritis:

- It usually occurs on top of post-menopausal atrophy of the endometrium which is infiltrated by numerous lymphocytes and plasma cells.
- It is a common cause of postmenopausal bleeding.

2- Chronic specific endometritis:

- Tuberculous endometritis:

- It is usually secondary to tuberculous salpingitis.
- The endometrium is infiltrated by multiple tubercles.
- If the patient is menstruating the tubercles are shed each month.

Chapter 9: Diseases of the female genital tract

- o In some cases menstruation ceases and caseation occurs.
- o It usually leads to sterility.

Fungal infection: *Actinomyces Israeli*, is common with intrauterine device (IUD).

Pyometria:

- It refers to the accumulation of pus within the endometrial cavity.
- It is the consequence of combined effect of obstruction and infection.
- It may be due to carcinoma or benign cervical stricture originating from senile atresia, surgery or cauterization.

Normal phases of the endometrium:

The endometrial changes that occur during the menstrual cycle reflect the rise and fall in the levels of ovarian hormones.

The normal phases of the endometrium are:

1. Menstrual or bleeding phase. (3 - 5 days).
2. Proliferative phase: (4th - 14th day) characterized by mitotic activity of both glandular and stromal cells.
3. Secretory phase: (17th - 28th day of the cycle).
 - ◀ Starts by basal vacuolation of the glandular epithelium (denoting the occurrence of ovulation).
 - ◀ Enlarged tortuous glands.
 - ◀ Active secretion in the glands lumina.
 - ◀ Stromal edema and predecidual reaction.
 - ◀ Leucocytic infiltration: Neutrophilic infiltration starts 2 days before the onset of the flow.

Endometriosis:

It is the presence of endometrial tissue (glands and stroma) in a location outside the endometrium.

Etiology: It is due to either:

1. Regurgitation theory; proposes menstrual back flow through the fallopian tube and subsequent implantation.

2. Metaplastic theory; proposes endometrial differentiation from coelomic epithelium.

Both of the above theories cannot explain lesions in lungs and lymph nodes.

3. Vascular or lymphatic dissemination theory; has been evolved to explain the extrapelvic or intranodal implants (**Fig. 9.14**).

According to the site, endometriosis may be:

Pelvic endometriosis:

1. Ovarian endometriosis: Is not a rare lesion, it may cause chocolate cysts in the ovary due to periodic bleeding with every menstrual cycle at the sites of ovarian endometriosis.
2. Other sites include; cervix, tubes, uterine ligaments, vagina, rectovaginal wall and pelvic peritoneum.

Extrapelvic endometriosis as in laparotomy scars, umbilicus, vulva, appendix etc...

Effects: - Severe dysmenorrhea (pain during menstruation) and pelvic pain.

- A common cause of infertility.

extra pelvic or tubal when it bleeds a mother

Adenomyosis:

It is the presence of endometrial tissue (glands and stroma) in a location outside the endomyometrium. (deep in myometrium)

- Nests of stroma or/and glands are seen deep in the myometrium (**Fig. 9.15**). *imagination*
- Because the glands in adenomyosis derive from basal layer, they do not undergo cyclic bleeding.
- It causes uterine enlargement, dysmenorrheal and pelvic pain before menstruation. *infertility*

Endometrial hyperplasia: ~

A common disease which usually occurs above the age of 35 years.

Aetiology:

It is due to prolonged excess estrogen relative to progesterin, inducing exaggerated endometrial proliferation (hyperplasia).

Chapter 9: Diseases of the female genital tract

Causes of excess estrogen are:

- Failure of ovulation with abnormal persistence of Graafian follicle.
- Prolonged administration of estrogenic steroids.
- Estrogen producing ovarian lesions (Polycystic ovary and granulosa-theca cell tumours of the ovary).
- Obesity as adipose tissue converts steroid precursors into estrogens.

Gross: The uterus is slightly or moderately enlarged, the endometrium is thickened, abundant and polypoid (**Fig. 9.9**).

Microscopic:

1. Simple hyperplasia:

- The hyperplastic glands are increased in number and lined by one or more layers of columnar epithelium.
- The glands are of variable sizes and some are cystically dilated (Swiss cheese appearance).
- The stroma is cellular with some mitotic activity (**Fig. 9.11**).

2. Complex hyperplasia:

- The glands are crowded i.e. back to back arrangement, with complex glandular architecture in the form of outpouching and infolding (**Fig. 9.12**).

3. Atypical hyperplasia:

- The hyperplasia is accompanied by cellular atypia (**Fig. 9.13**).

NB:

- All types of hyperplasia produce abnormal uterine bleeding
- Only atypical hyperplasia is associated with a greater risk for progression to carcinoma.



Fig.9.10: endometrial hyperplasia

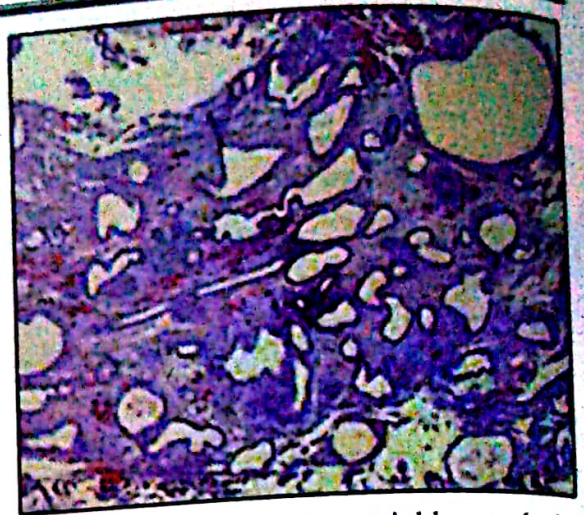


Fig.9.11; Simple endometrial hyperplasia

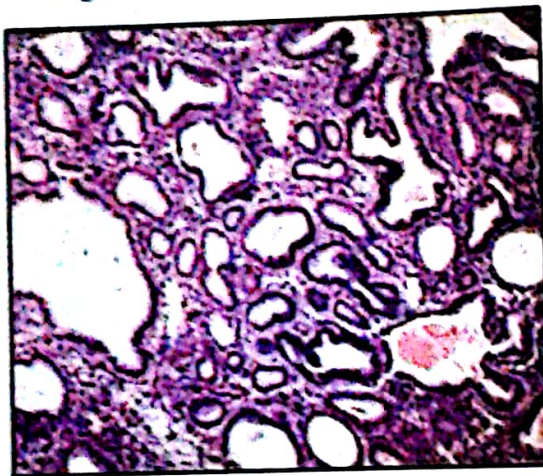


Fig.9.12; Complex endometrial hyperplasia

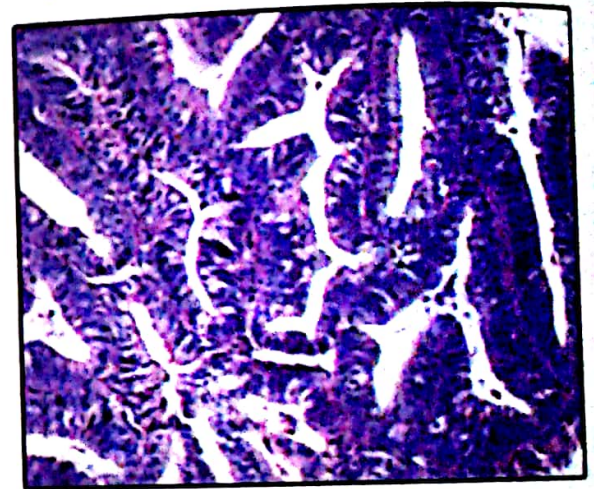


Fig.9.13; Atypical endometrial hyperplasia

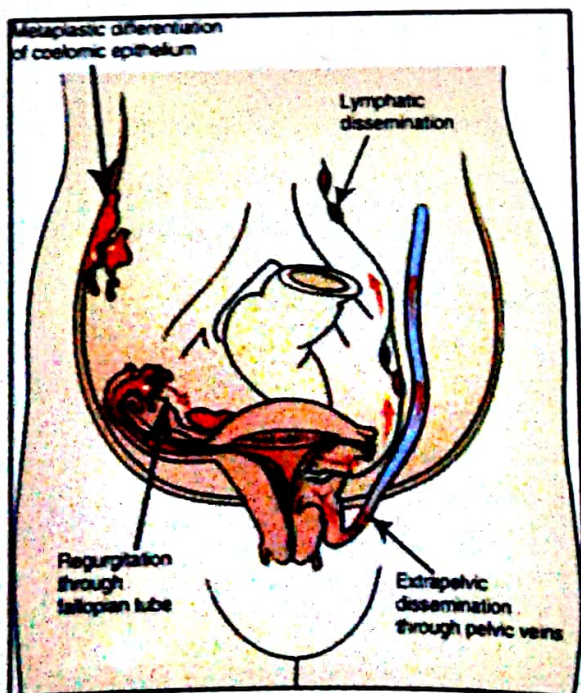


Fig.9.14: Theories of endometriosis.

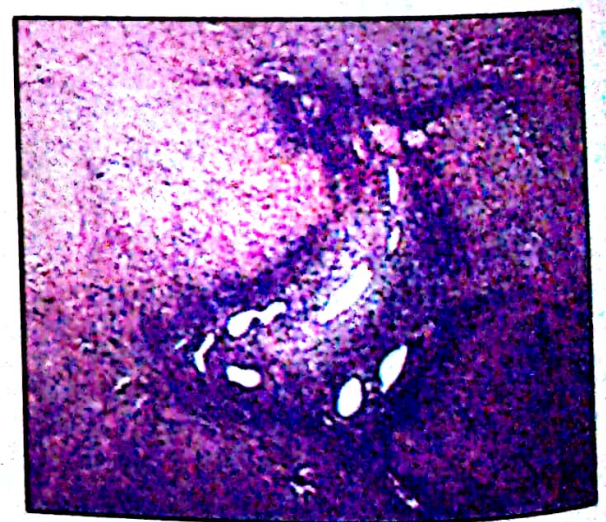


Fig.9.15: Adenomyosis.

Tumours of the body of the uterus

Classification:

Benign: Endometrial Polyp
Leiomyoma.

Malignant

A- Primary malignant tumours:

1. Carcinoma of the endometrium. *placental*
2. Mesenchymal tumours.
 - a- Leiomyosarcoma.
 - b- Malignant mixed mesodermal tumours.
 - c- Endometrial stromal sarcoma.

B- Metastatic tumours. *breast, colon, ov*

Endometrial Polyp:

- ☐ It is a benign polypoid mass that arises from endometrial mucosa.
- ☐ Can occur any age but most commonly around the time of menopause.
- ☐ May cause irregular uterine bleeding.
- ☐ Rare malignant transformation.

Leiomyoma:

- ☐ They are the most common tumour in women which arise from the muscles of the uterus.
- ☐ Affect 30-50% of women during the active reproductive life.
- ☐ They are related to oestrogenic stimulation.

Gross:

- The uterus is usually enlarged. It may be uniform or more common irregular and firm in consistency.
- Leiomyomas are sharply circumscribed greyish white, rounded nodules with whorly cut surface (*Fig. 9.16a*).
- They may occur single or more often multiple.
- The apparent encapsulation is due to compression of the adjacent muscles.
- Large tumours may show cystic degeneration, and calcification.
- They may occur within the myometrium (interstitial) or (submucous) protruding into the uterine cavity or (subserous) beneath the serosal covering.

Microscopic:

- Leiomyoma consists of interlacing bundles of smooth muscle fibers with dense collagenous bundles.
- The stroma is vascular (Fig 9.16b).

Pathological changes and effects:

1. Hyaline change and cystic degeneration.
2. Necrosis may occur due to deficient blood supply especially in the center of large leiomyoma. A pedunculated tumour may undergo torsion of the pedicle followed by necrosis.
3. Infection and suppuration rarely occur in submucous leiomyoma.
4. Pathological calcification in old lesions.
5. Red degeneration: It is often associated with pregnancy or the use of oral contraceptive pills. The leiomyoma becomes soft, haemorrhagic and infarcted due to thrombosis of the vessels or twisting of the pedicle. Clinically patients may complain of abdominal pain vomiting and fever.
6. Malignant change into leiomyosarcoma is extremely rare.

Clinical: Leiomyomata may be symptomatic or associated with:

1. Uterine bleeding.
2. Urinary bladder disorders.
3. Impaired fertility.
4. Spontaneous abortion, fetal malpresentation and postpartum haemorrhages.

NB: Leiomyoma of the cervix is less common, usually solitary and may obstruct the cervical canal.

Carcinoma of endometrium:

- It is the most common invasive cancer of the female genital tract usually develops after the menopause (55 - 65 years).
- Endometrial carcinoma comprises two distinct types:
 - 1- **Endometrial type (80%):** Related to excess estrogen and endometrial hyperplasia and mutation in DNA mismatch repair genes.
 - 2- **Serous type:** Arise in the setting of endometrial polyp and show mutation in P53.

Risk factors of endometrioid carcinoma:

1. Prolonged oestrogen stimulation as in endometrial hyperplasia.
2. Infertility.
3. Diabetes.
4. Hypertension.
5. Obesity.

Gross: It presents either as:

1. Localized polypoid mass.
2. Diffuse spreading lesion involving the entire endometrial surface which becomes irregular, ulcerated and necrotic.

Microscopic:

1. **Endometrioid carcinoma:**

- It resembles the normal endometrial glands and are graded I-III.
- It may show squamous differentiation. If the squamous elements are benign it is called **adenoacanthoma (Fig.9.17)**. But if the squamous elements are malignant it is called **adenosquamous carcinoma**.
- It may also show mucinous or secretory differentiation.

2. **Serous carcinoma:** Form small tufts and papillae. They are highly aggressive (Fig.9.18).

Clinical manifestation:

- Leucorrhea and irregular uterine bleeding in postmenopausal females.
- Symptoms of spread (local, lymphatic and distant metastasis)

Leiomyosarcoma:

- Leiomyosarcoma arises de novo from the myometrium and not from a pre-existing leiomyoma.
- Commonly occurring in postmenopausal women.

Gross: The uterus is enlarged and soft.

The tumour forms a solitary bulky fleshy mass that invade the uterine wall or project into the uterine cavity as a polypoid mass (Fig.9.19a).

Microscopic:

- It varies from tumours resembling leiomyoma to widely anaplastic neoplasms (Fig.9.19b).
- Can be differentiated from benign leiomyoma by the presence of: necrosis, cytology atypia and mitotic activity.

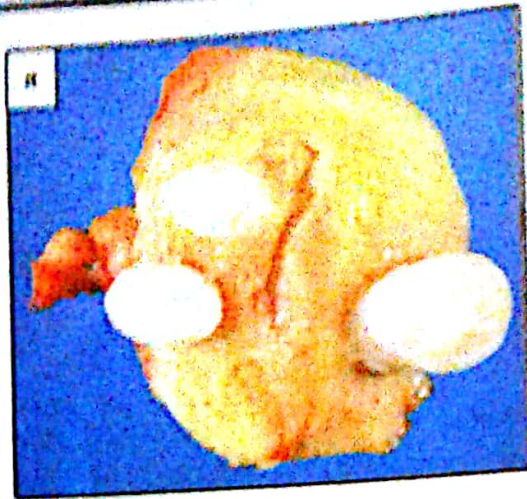
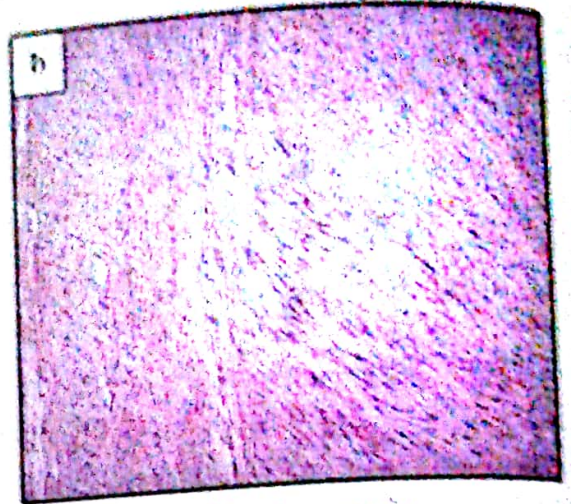


Fig. 9.16: Leiomyomata (a) gross



(b) microscopic

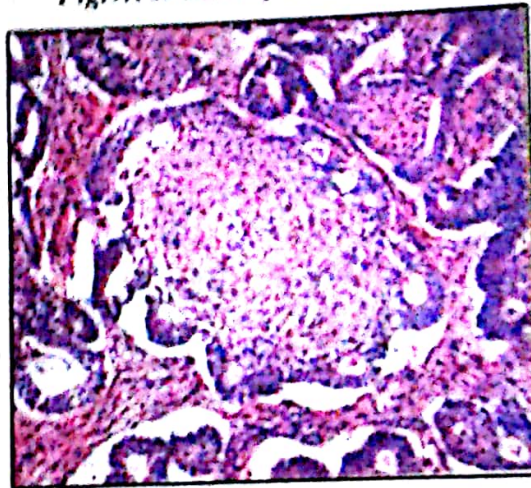


Fig. 9.17: Endometrioid carcinoma with squamous differentiation

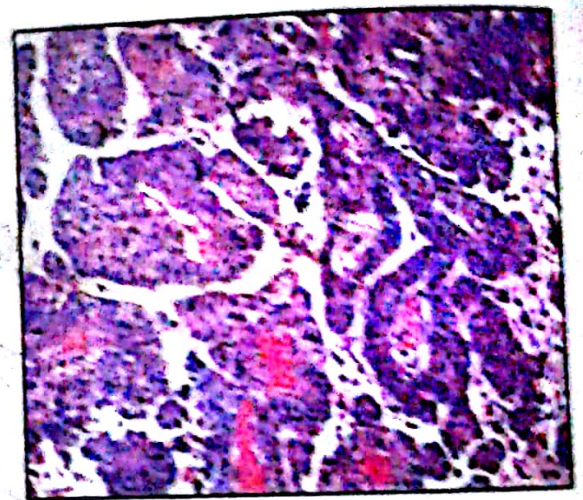


Fig. 9.18: Serous carcinoma of the endometrium

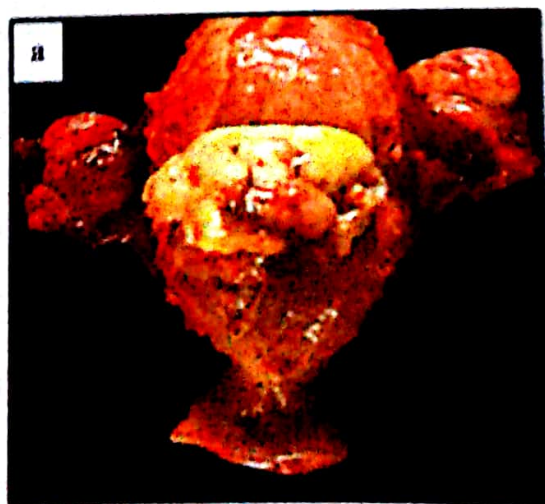
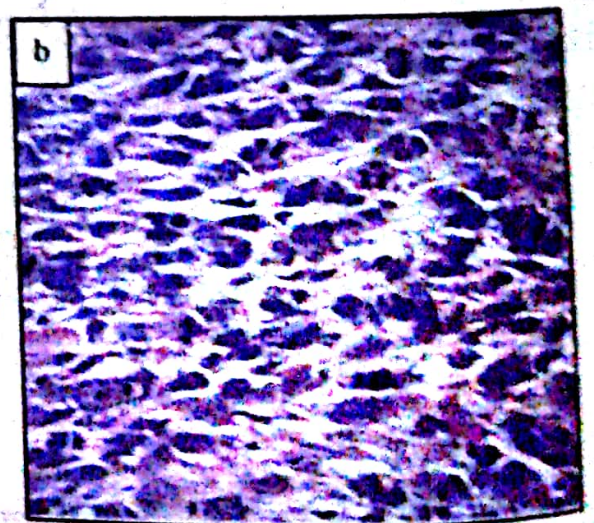


Fig. 9.19: Leiomyosarcoma (a) gross



(b) microscopic

Gestational trophoblastic diseases:

Definition: A group of diseases characterized by abnormal proliferation of trophoblastic epithelial covering of chorionic villi.

Classification:

1 Gestational trophoblastic diseases are divided into three categories:

- Hydatidiform mole.
- Invasive mole.
- Choriocarcinoma.

2 They range in aggressiveness from benign hydatidiform moles to highly malignant choriocarcinomas.

3 All Gestational trophoblastic diseases release **human chorionic gonadotrophin (HCG)**.

- HCG can be detected in the circulating blood and urine at titers considerably higher than those found during normal pregnancy.
- HCG titers shows progressive rise from hydatidiform mole to invasive mole to choriocarcinoma.
- In addition to aiding diagnosis, the fall or rise in the level of the HCG in the blood or urine can be used to monitor the effectiveness of treatment.

I. Hydatidiform Mole (Molar pregnancy):

Definition: It is a voluminous mass of swollen, sometimes cystically dilated chorionic villi, appearing grossly as grapelike structures. The swollen villi are covered by varying amounts of normal to highly atypical chorionic epithelium. *Considering a normal pregnancy, than*

- Two distinct types of hydatidiform mole are recognized: *complete and partial moles.*
- The two patterns result from abnormal fertilization.

A- Complete Mole

- It results from the fertilization of an empty (dead) egg by two spermatozoa (each is 23 chromosomes), yielding a diploid karyotype (46 chromosomes) composed of entirely paternal genes (**Fig. 9.20**).
 - It does not permit embryogenesis and therefore never contains fetal parts.
- 10- Cases*

Gross:

- The uterus is usually enlarged.
- The uterine cavity is filled with a mass of grape- like structures of thin walled translucent greyish white cysts (**Fig.9.21a**).
- The weight of this evacuated mass is usually in excess of 200g.
- No fetal parts are identified.

Microscopic:

- The cysts are composed of hydropic swelling of chorionic villi, the interior being filled with an avascular loose myxoid stroma.
- Trophoblastic proliferation produces hyperplastic sheets of cytotrophoblastic and syncytiotrophoblastic cells (**Fig.9.21b**).
- Cytologic atypia may be present.

Clinical features:

1. Positive pregnancy test.
2. Uterine enlargement is usually greater than of normal pregnancy.
3. Vaginal bleeding, usually begins in the third to fourth month.
4. Greatly elevated levels of HCG in serum.

Complications:

1. Choriocarcinoma in about 2.5% of cases.
2. Invasive mole in about 10% of cases.

The most precise method of detecting complications after molar pregnancy is following up of serum HCG level.

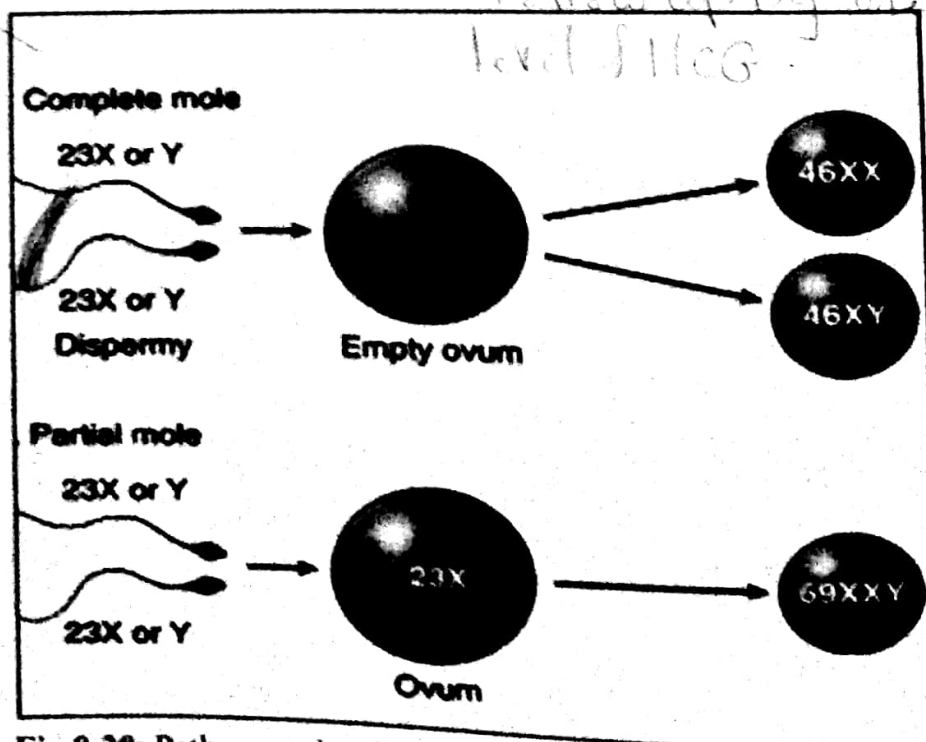


Fig.9.20: Pathogenesis of vesicular mole (complete and partial).

Chapter 9: Diseases of the female genital tract

B. Partial mole:

- It results from the fertilization of a normal egg (23 chromosomes) by two spermatozoa (each is 23 chromosomes), resulting in a triploid (69 chromosomes) karyotype (*Fig.9.20*).
- It is compatible with early embryo formation and therefore contains fetal parts.

Gross: The uterus may be enlarged. Few vesicles and fetal parts are usually seen (*Fig.9.22a*).

Microscopic: The villous edema involves only a proportion of villi, and the trophoblastic proliferation is focal and slight (*Fig.9.22b*).

Clinical features; are similar to those of complete mole but the serum level of HCG is not greatly elevated.

Partial moles have a minimal risk for complication (*Table.9.1*).

Application: minimal change after to
Table.9.1: Features of complete and partial hydatidiform mole

	Hydatidiform Mole	Partial mole
Cause	Fertilization of an empty egg by two sperms	Fertilization of a normal egg by two sperms
Fetal parts	Never present	Present
Karyotype	Diploid (46,XX) , (46,XY)	Triploid (69, XXY)
Villous edema	All villi	Some villi
Trophoblastic Proliferation	Diffuse & circumferential	Focal & slight
Atypia	Often present	Absent
Serum hCG	++++	+
Risk of chorio-carcinoma	2.5%	Rare

II. Invasive mole: (chorioadenoma destruens):

- It is a mole that penetrates and may even perforate the uterine wall.
- Marked by active proliferation of both cyto and syncytiotrophoblasts.
- But it does not metastasize.

Effects:

1. Uterine bleeding, sometimes life-threatening with rupture uterus.
2. Abortion.
3. High level of human chorionic gonadotrophic hormones (HCG) in urine.

III. Choriocarcinoma:

It is a rare malignant tumor that arises from the epithelial tissue covering the chorionic villi and less commonly from the totipotent cells of the gonads.

About half the cases are preceded by hydatidiform mole.

Gross: The tumor appears as a large, hemorrhagic and necrotic mass. It invades and destroys the uterine wall (**Fig. 9.23a**).

Microscopic:

- The tumor is formed of the two elements of the chorionic epithelium. Large masses of rounded or polyhedral **Langhans cells** and **syncytial trophoblastic cells** are usually seen invading the uterine wall, blood vessels and lymphatics (**Fig. 9.23b**).
- There is neither stroma nor blood vessels, but areas of necrosis and extravasated blood are usually present.
- Chorionic villi are not formed.

Spread:

1. Local infiltration.
2. Blood spread, rapidly and early to the lungs, vagina, vulva, liver ... etc.

N.B.: Despite the extremely aggressiveness of these neoplasms, placental choriocarcinomas are **remarkably sensitive to chemotherapy**. Nearly 100% of cases can be cured, even those with metastasis at distant sites as the lungs.

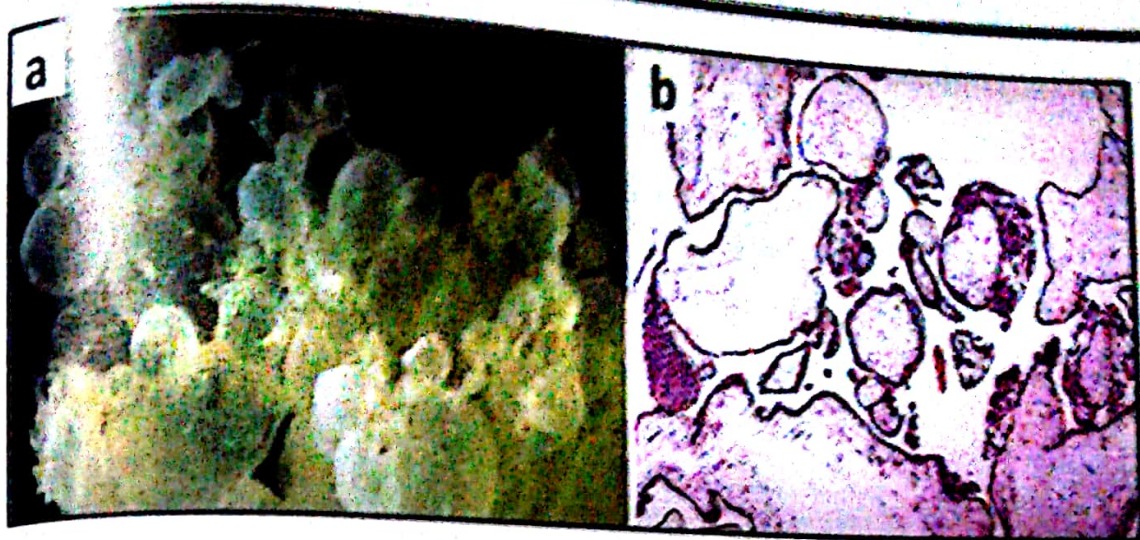


Fig.9.21: Complete mole (a) gross.

(b) microscopic

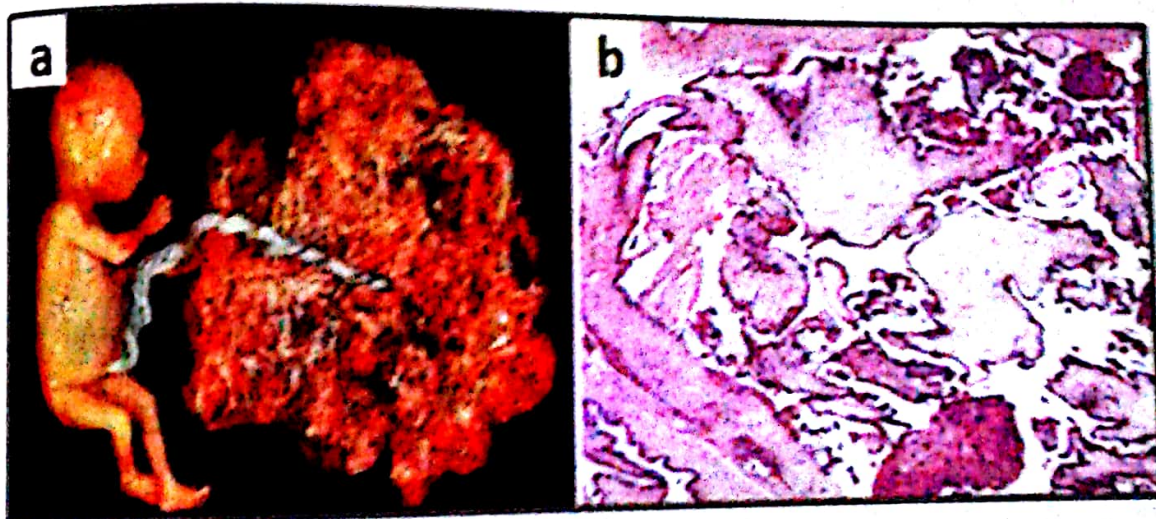


Fig.9.22: Partial mole (a) gross

(b) microscopic

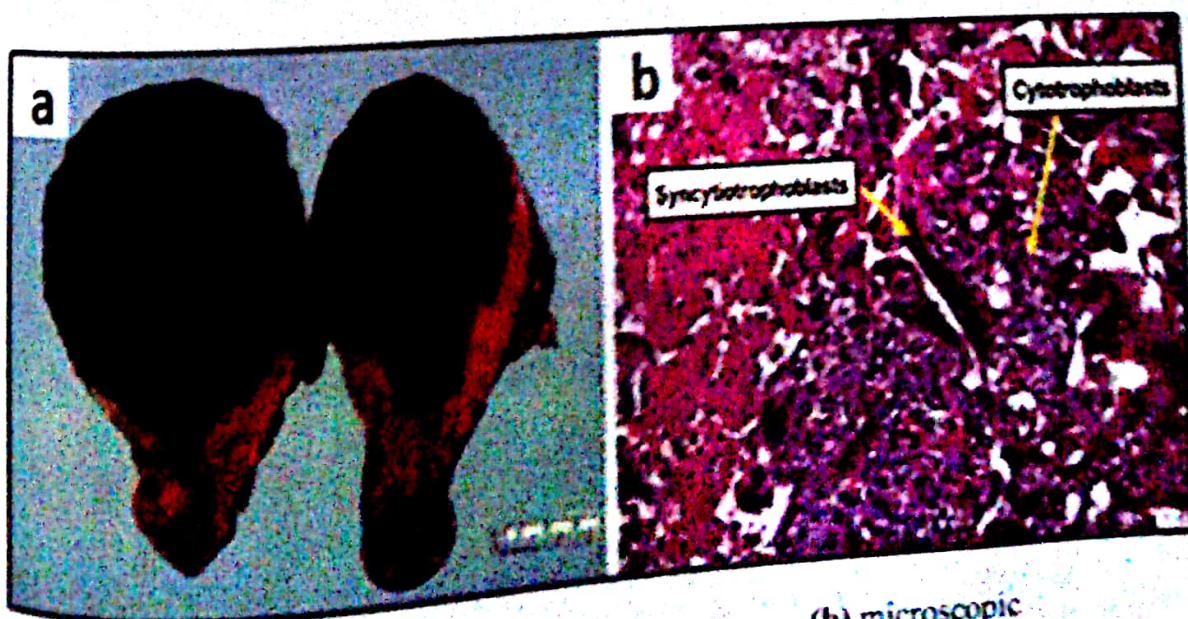


Fig.9.23: Choriocarcinoma (a) gross.

(b) microscopic

Chapter 9: Diseases of the female genital tract

Causes of abnormal uterine bleeding by age groups

Age Group	Cause(s)
Prepuberty	- Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle
Reproductive age	- Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy). - Organic lesions (<u>leiomyoma</u>, <u>adenomyosis</u>, <u>polyps</u>, <u>endometrial hyperplasia</u>, <u>carcinoma</u>). - Anovulatory cycle. - Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase).
Perimenopause	- Anovulatory cycle. - Irregular shedding. - Organic lesions (carcinoma, hyperplasia, polyps)
Postmenopause	- Organic lesions (carcinoma, <u>hyperplasia</u>, polyps) - Endometrial atrophy.

Diseases of the fallopian tubes

Salpingitis: (inflammation of fallopian tubes).

Acute salpingitis:

- ☐ This is a purulent inflammatory process usually secondary to introduction of bacteria from the uterine cavity into the tubal lumen.
- ☐ Neisseria gonorrhea is the most common causative organism. Other aerobic and anaerobic bacteria have been also implicated.
- ☐ Introduction of bacteria is increased with intrauterine devices, after delivery and after surgical procedures such as uterine curette.

Gross: The tubes are swollen and congested and the lumen is filled with pus. **Microscopic:** The tubes show an acute inflammatory reaction with many polymorphs and pus cells.

Chronic salpingitis:

- ☐ If acute salpingitis does not resolve or with repeated infections, chronic salpingitis ensues.
- ☐ The tube is distended, irregular in shape with many fibrous adhesions over its serosal surface. Healing and organization leads to permanent

bridging between plicae and the wall is infiltrated by lymphocytes and plasma cells.

Complications of salpingitis:

1. Extension of infection through the fimbrial end of the tube to the peritoneum leading to pelvic peritonitis that may become generalized.
2. Extension of infection to the near-by ovary leading to a tubo-ovarian abscess.
3. Chronicity, and if infection is mild it may lead to hydrosalpinx while if severe it leads to pyosalpinx.
4. Sterility, particularly if bilateral.
5. Ectopic pregnancy.

Hydrosalpinx:

- It is characterized by obliteration of the fimbriated end with dilatation of the tube.
- The wall is whitish, thin and translucent and the tube contains clear serous fluid.

Pyosalpinx:

It has the same pathogenesis of hydrosalpinx but here the lumen is distended with pus and the wall is thickened and opaque.

Tuberculous salpingitis:

- o TB of female genitalia is secondary to a primary infection elsewhere.
- o For unknown reason; blood-borne organism preferably lodges in the tubes.
- o Lymphatic spread from intestinal tuberculosis or direct spread from bladder or intestinal tuberculosis may occur.

Gross; the tube is elongated, nodular, irregularly distended, with adhesions to near-by structures and showing serosal tubercles.

Microscopic; the picture is that of a caseating granuloma.

Tubal pregnancy:

Ectopic pregnancy refers to the implantation of fertilized ovum outside its normal location within the uterine cavity. The most common site is the tube (tubal pregnancy).

Pathogenesis:

1. Factors that retard the passage of the conceptus along the tube as chronic salpingitis and congenital tubal diverticulae.
2. Factors that increase tubal receptibility as in endometriosis with attraction of the fertilized ovum to this site.

Gross; The tube is distended by a haemorrhagic clot enmeshing chorionic villi.

Fate: Most ectopic pregnancies terminate by tubal abortion or perforation with release of blood into the peritoneal cavity and subsequent intraperitoneal haemorrhage.

Tumours of fallopian tubes:

- a- **Benign tumours:** rare, as fibroma, leiomyoma, haemangioma, etc....
- b- **Malignant tumours:** rare, mainly adenocarcinoma and sarcoma.

Diseases of the ovaries

Inflammatory diseases of the ovary:

1- Tubo-ovarian abscess:

- Infection of the fallopian tube results in destruction of its normal architecture and its adherence to the ovary.
- As the infection progresses it can bind the two organs together in a distorted mass.

Gross; the cut surface reveals a fibrotic wall and a cavity containing purulent material (Fig.9.24).

Microscopic; necrosis, granulation tissue with inflammatory cell infiltration.

2- Chronic granulomatous oophritis:

Tuberculosis and bilharziasis are rare causes of granulomatous oophritis.

Cysts of the ovaries:

- Cysts are the most common cause of enlarged ovaries.
- Cysts can be divided into those arising from ovarian follicles (non-neoplastic or functional) and those arising from epithelial lining.

Non-neoplastic cysts:

1. Follicular cyst:

- It originates from unruptured Graafian follicles or in follicles that have ruptured and immediately sealed.
- Follicular cysts are very common and may be considered physiologic.
- It can occur at any age.

Gross:

- Unilocular cyst varying in size from 1 to 5 cm. either single or multiple, unilateral or bilateral.
- The outer surface is smooth, the wall is thin and the cyst contains a clear watery fluid (Fig.9.26a).

Microscopic:

It is lined by granulosa cells surrounded by theca interna cells. (Fig.9.26b).

Clinical:

- Occasionally, become palpable masses and produce pelvic pain.
- They may be oestrogen secreting causing menstrual irregularities.

2. Corpus luteum cyst:

It results from delayed resolution of a corpus luteum.

Gross: Unilocular, small cyst (3-6 cm in diameter) with a yellow festooned lining (Fig.9.25).

Microscopic: lined by luteinized granulosa cells. They may be hemorrhagic.

Clinical: They secrete excess progesterone, and may lead into menstrual irregularities.

3. Theca Lutein cyst:

- They are associated with high level of circulating gonadotropin as in pregnancy, hydatidiform mole, choriocarcinoma and in patients receiving gonadotropin therapy. The excessive gonadotropin leads to hyperplastic and luteinized theca interna cells.
- Hemorrhage and rupture may require surgical intervention.



Fig. 9.24: Tuboovarian abscess



Fig. 9.25: Corpus luteum cyst

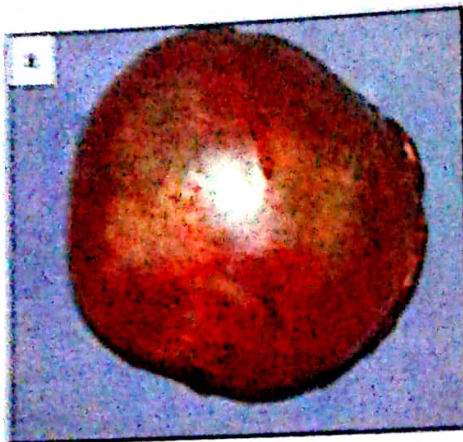


Fig. 9.26: Follicular cyst (a) gross



(b) microscopic



Fig. 9.27: Polycystic ovary



Fig. 9.28: Chocolate ovarian cyst

Polycystic ovarian disease (PCOS):

It is a disorder in which multiple cystic follicles in the ovaries produce excess androgens and estrogens. Affected teenage girls present with oligomenorrhea, hirsutism, infertility and sometimes obesity.

Gross:

- Both ovaries are uniformly involved and they are 2-5 times the normal size.
- The ovaries show a thickened capsule and are studded by multiple small cysts 0.5 to 1.5 cm in diameter (**Fig.9.27**).

Microscopic:

- They show a thickened tunica albuginea with cystic follicles lined with granulosa cells with hyperplastic luteinized theca interna.
- There is no corpora lutea with no or rare corpora albicantia.

Clinical manifestations:

1. **Hyperoestrinism:** resulting in endometrial hyperplasia and abnormal uterine bleeding.
2. **Stein-Leventhal syndrome:** characterized by secondary amenorrhea, sterility and polycystic ovarian disease.
3. **Virilism:** manifested by hirsutism of a progressive nature, voice changes and breast atrophy.

Ovarian endometriosis:-

- Early, it may appear as punctate red brown spots or patches associated with dense fibrous adhesions.
- **Endometriotic chocolate cysts** due to repeated hemorrhages in the ovaries, either partially or totally.
 - The cyst wall is thick and fibrotic, with a smooth or shaggy red brown inner lining and covered by dense fibrous adhesions.
 - The cyst contents are red brown chocolate material (**Fig.9.28**).

Ovarian neoplasms

Ovarian cancer accounts for 3% of all female malignancies.

It is a cause of high mortality from female genital cancer due to lack of methods of early detection.

Risk factors:

- Nulliparity.
- Family history.
- Germline mutation in tumour suppressor genes as BRACA 1&2.

Gross:

- Both ovaries are uniformly involved and they are 2-5 times the normal size.
- The ovaries show a thickened capsule and are studded by multiple small cysts 0.5 to 1.5 cm in diameter (**Fig. 9.27**).

Microscopic:

- They show a thickened tunica albuginea with cystic follicles lined with granulosa cells with hyperplastic luteinized theca interna.
- There is no corpora lutea with no or rare corpora albicantia.

Clinical manifestations:

1. **Hyperoestrinism:** resulting in endometrial hyperplasia and abnormal uterine bleeding.
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Risk factors:

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Classification:

Histological classification of ovarian tumors, based on the cell of origin:

1. Surface epithelial tumors:

- a- Serous tumors.
- b- Mucinous tumors.
- c- Endometrioid tumors.
- d- Clear cell tumors.
- e- Brenner tumors (Transitional cell tumours).

2. Sex-cord-stromal tumors:

- a- Granulosa -Theca cell tumors:
 - i. Pure granulosa cell tumor.
 - ii. Pure theca cell tumor (i.e. Thecoma).
 - iii. Mixed granulosa-theca cell tumor.
- b- Sertoli-leydig cell tumor:
 - i. Pure sertoli cell tumor.
 - ii. Pure leyding cell tumor.
 - iii. Mixed sertoli-leydig cell tumor.

3. Germ cell tumors:

- a- Dysgerminoma.
- b- Endodermal sinus Tumor.
- c- Embryonal carcinoma.
- d- Choriocarcinoma.
- e- Teratomas.
 - i. Mature.
 - a- Solid.
 - b- Cystic, mature cystic teratoma (dermoid cyst).
 - ii. Mature teratoma with malignant transformation.
 - iii. Immature.
 - iv. Monodermal and highly specialized:
 - a- Struma ovarii.
 - b- Carcinoid.
 - c- Struma ovarii and carcinoid.

4. Soft tissue tumors not specific to ovary.

5. Secondary (metastatic) Tumors.

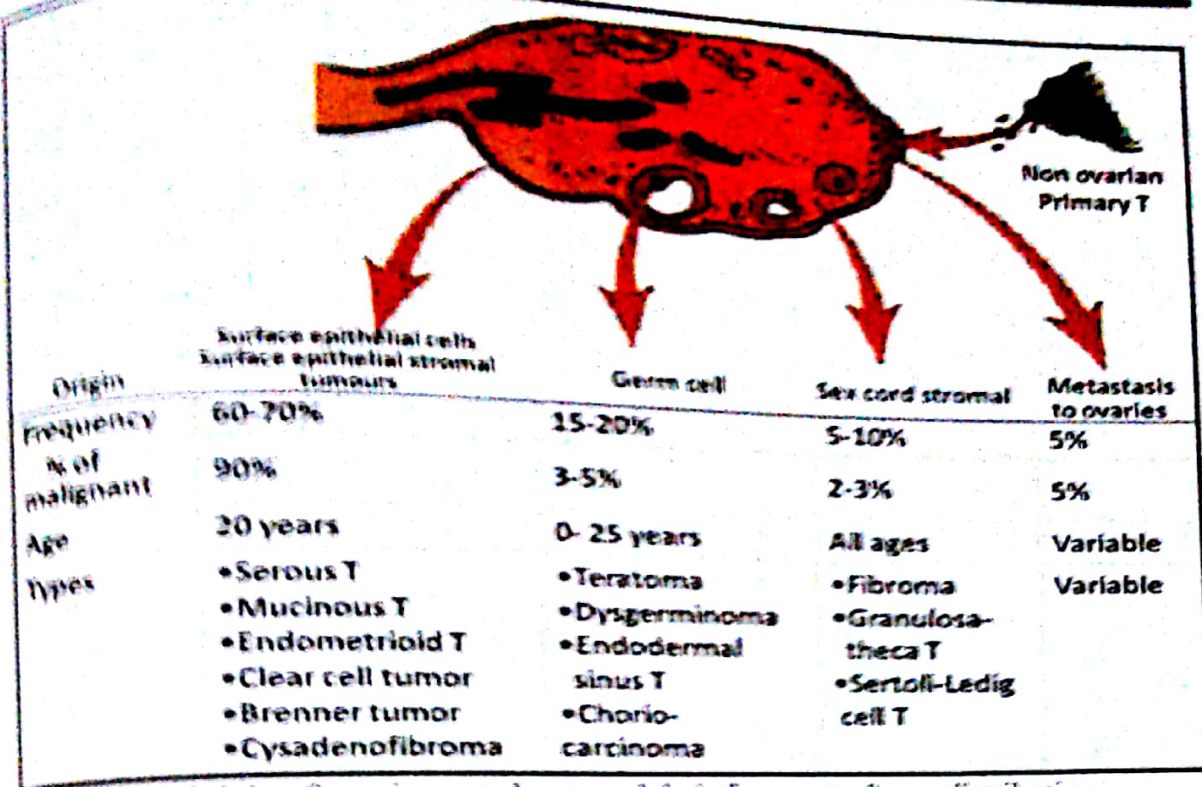


Fig. 9.29: Origin of ovarian neoplasms and their frequency & age distribution.

Surface-epithelial tumors:

- o These neoplasms are derived from the coelomic mesothelium that covers the surface of the ovary.
- o With repeated ovulation and scarring the surface epithelium is pulled into the cortex of the ovary, forming small epithelial cysts.
- o These can undergo metaplasia and neoplastic transformation into epithelial tumors of the various histologic types.

a- Serous Tumors:

They are the most common of the ovarian epithelial tumours.

They are classified into:

- Benign serous tumors (60%)
- Borderline serous tumors, of low malignant potential (15%).
- Malignant serous tumors (25%)

Benign serous cyst or serous cystadenoma:

Gross:

- Thin walled unilocular cysts distended with clear straw-colored fluid.
- The outer and inner surfaces are smooth.
- They are usually unilateral with a proportion being bilateral.

- They may have stromal fibrous component (serous cystadenofibroma).
- Papillary serous cystadenoma is a variant with papillae seen either on the inner (endophytic) or outer (exophytic) surface of the cyst (*Fig.9.30*).

Microscopic:

Benign tumors: The lining of the cyst is a single layer of cuboidal epithelium or columnar partially ciliated resembling those lining the fallopian tubes.

Border line tumors: There is cytological atypia of the lining cells with no stromal invasion.

Malignant tumors: Both stromal invasion and cytological atypia are seen. Psammoma bodies are common in the tips of papillae of malignant tumors.

B. Mucinous tumours:

They are classified into:-

- Benign mucinous tumor "mucinous cystadenoma" (80%)
- Borderline mucinous tumor (10%).
- Malignant mucinous tumor "mucinous cystadenocarcinoma" (10%).

Gross:

- They are ovoid or lobulated and may be very large.
- Usually, they are unilateral but occasionally bilateral.
- The outer surface is smooth and, the wall is fairly thick and fibrous.
- In its most typical form, it is multilocular with variable sized locules separated by fibrous tissue septa. It is filled with mucinous fluid (*Fig.9.31a*).

Microscopic:

Benign tumors: The cyst is lined by a single layer of tall columnar cells with basal nuclei and abundant slightly basophilic mucin containing cytoplasm, similar to those of the endocervical mucosa (*Fig.9.31b*).

Borderline tumors: Show cytological atypia of the lining cells.

Malignant tumors: Are characterized by both stromal invasion and cytological atypia.

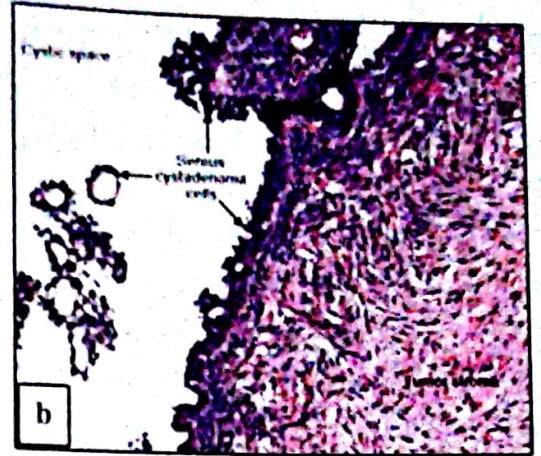
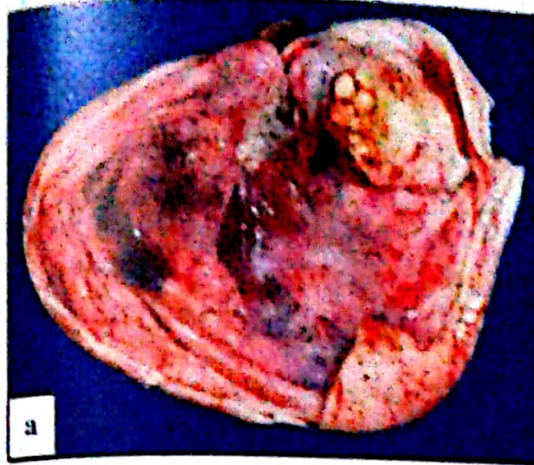


Fig.9.30: Papillary serous cystadenoma (a) Gross (b) Microscopic

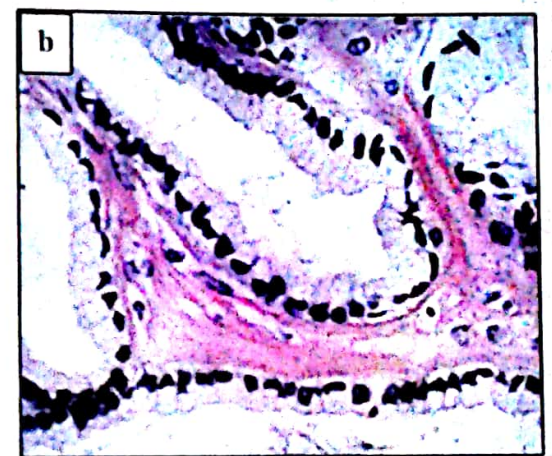
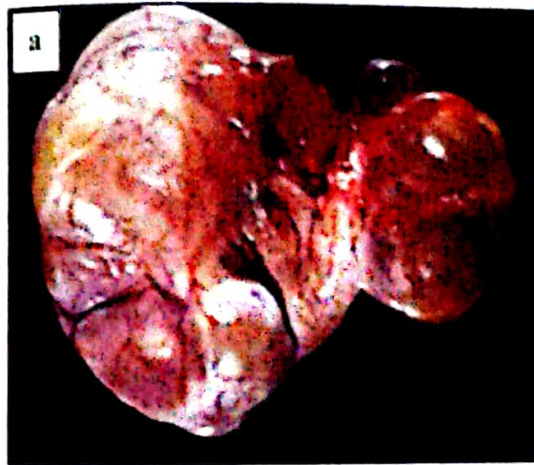


Fig.9.31: Mucinous cystadenoma (a) Gross (b) Microscopic

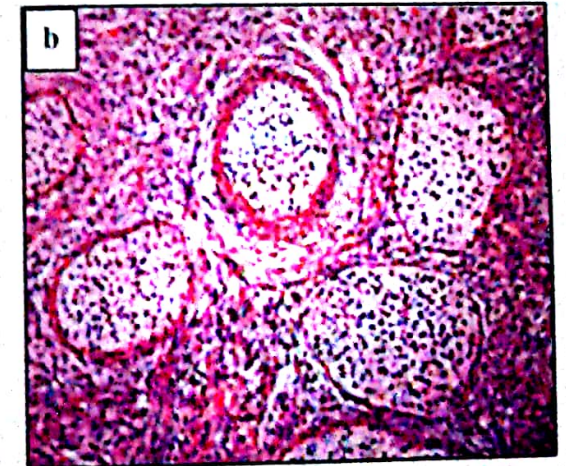
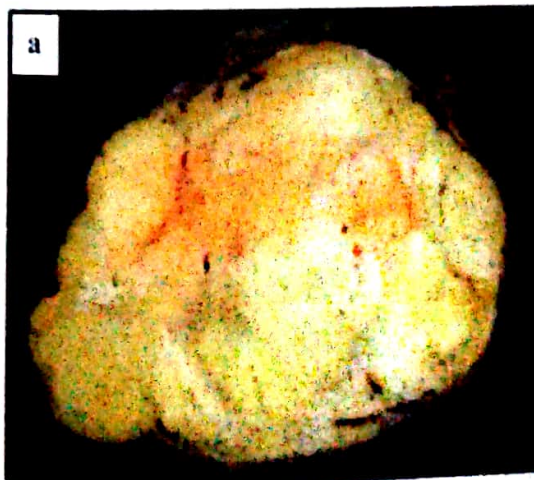


Fig.9.32: Brenner tumour (a) gross (b) microscopic

C. Endometrioid Tumors:

Although benign and borderline endometrioid tumors exist, endometrioid tumors of the ovary are usually malignant.

D. Brenner tumors (Transitional cell tumors):

These are rare tumors derived from the surface epithelium (coelomic), which undergoes metaplasia to form the typical urothelial lining.

Gross:

- Most are unilateral, ranging from few centimeters up to 20 cm in diameter.
- Most are circumscribed, solid, firm and rubbery (Fig.9.32a).
- Less commonly, they may have cystic component.

Microscopic: Nests of transitional epithelial nests in a fibrous stroma (Fig.9.32b).

Most are benign, but malignant and borderline tumours have been described.

Malignant surface epithelial tumors:

Gross:

- o They may be cystic, solid, or partly cystic and partly solid.
- o Papillary growths could be seen, either internally (endophytic) or externally (exophytic).
- o The contents of the cystic spaces are serous, mucoid and or hemorrhagic. Areas of necrosis and hemorrhage are common.

Microscopic: They are usually adenocarcinoma with different grades of differentiation, labelled according to the cell of origin into serous (Fig.9.33), mucinous, endometrioid and clear cell.

The spread of malignant ovarian tumors: local, via lymphatics and blood.

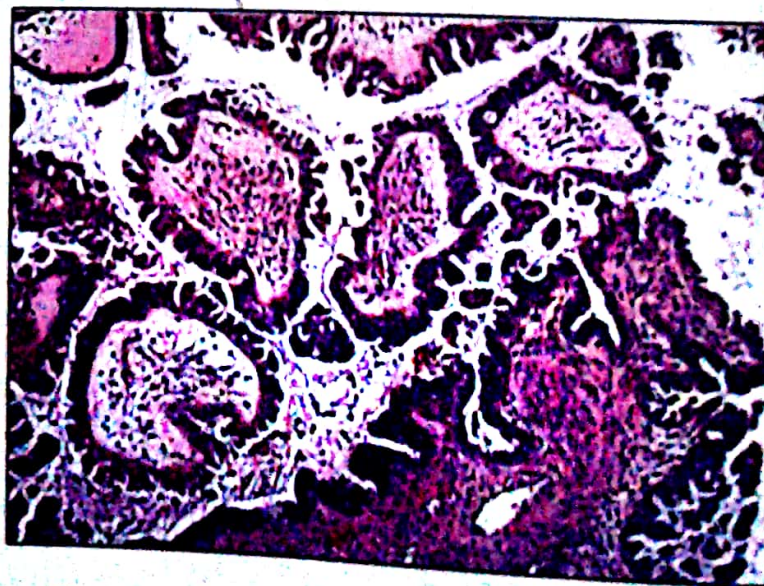


Fig.9.33: Malignant papillary serous cystadenoma.

Sex-cord-stromal tumors

A. Granulosa cell tumors:

- ☐ They are common in postmenopausal females, but can occur at any age.

Gross:

- They are usually unilateral, rarely bilateral.
- They range in size from microscopic to huge tumors filling the pelvis.
- Most tumors are solid (Fig. 9.34a), may be partly cystic and few are totally cystic; unilocular or multilocular.

Microscopic:

- o Composed of cuboidal cells with a nuclear longitudinal groove (coffee-bean nucleus) and are arranged in different patterns:
 - Trabecular.
 - Insular (i.e. in compact groups).
 - Microfollicular (Fig. 9.34b)
 - Diffuse sarcomatoid (i.e. sarcoma-like).

Clinical features:

Granulosa cell tumors are oestrogen-producing tumors (feminizing) which effects are dependent on the age of the patient:

- a- In pre-menarchal period: It leads to precocious pseudopuberty i.e. abnormal menstruation and development of secondary sexual characters.
 - b- In reproductive period: There is disturbance of menstruation with abnormal bleeding, endometrial hyperplasia, uterine leiomyoma, fibrocystic disease and carcinoma of breast.
 - c- In post-menopausal period: Abnormal bleeding ensues with the possibility of endometrial hyperplasia and carcinoma.
- In all age groups, all these manifestations disappear after removal of the tumor.

The biological behavior of such tumors is unpredictable; sometimes they behave in a benign fashion, in others they behave in a malignant fashion (i.e. potentially malignant).

B. Theca cell tumors (thecoma):

They are oestrogen producing tumors as granulosa cell tumors.

Gross:

- ☐ They are nearly always unilateral.

- Solid masses, firm and rubbery in consistency, greyish-white with yellow tinge (**Fig.9.35a**).

Microscopic:

- o Composed of spindle-shaped theca cells arranged in a fibroma-like pattern.
- o Foci of luteinization are seen, hence the yellow tinge (**Fig.9.35b**).

C. Sertoli cell tumors:

Gross: They are lobulated solid tumors, firm in consistency and yellow to orange in color.

Microscopic: Formed of tubules lined by a single layer of cells with a clear cytoplasm and basal nuclei.

D. Leydig cell tumors:

Gross: Small solid tumors with a yellow tinge.

Microscopic: Formed of sheets of Leydig cells showing an eosinophilic cytoplasm that is finely vacuolated.

Clinical:

- o Sertoli-Leydig cell tumors secrete testosterone leading to defeminization i.e. amenorrhea and atrophy of breast, followed by masculinization i.e. hirsutism, enlargement of clitoris and male voice.
- o They are rarely malignant.

Germ cell tumors:

A. Teratomas: (**Fig.9.36a,b**). See General Pathology

B. Dysgerminoma:

Gross: They are usually large tumors, solid and firm with a pink-grey color.

Microscopic: Composed of immature cells with central nuclei, prominent nucleoli arranged in cords or groups. These are supported by a fibrous tissue stroma infiltrated by lymphocytes.

C. Endodermal Sinus Tumor (yolk sac tumor):

It is malignant germ cell tumor with extra-embryonic differentiation. Occurs predominantly in young females, between 10 - 20 years.

Gross: They are usually large tumors, with a nodular cut surface, grey-white in colour, firm to rubbery in consistency.

Microscopic:

- Microcystic pattern formed by a loose network of flat or cuboidal cells.
- Schiller-Duval body is pathognomonic; central blood vessel enveloped by germ cells within a space similarly lined by germ cells, resembles glomerulus
- **Alpha-fetoprotein (AFP)** tumor marker is markedly raised (**Table.9.2**).

D. Embryonal carcinoma:

Gross: A solid, grey-white mass; with areas of necrosis and hemorrhage in larger tumors.

Microscopic: Composed of solid aggregates of epithelial-like cells with hyperchromatic and/or vesicular nuclei showing prominent nucleoli.

N.B.: It usually contains elements of choriocarcinoma and/or endodermal sinus tumors in this case the serum NCG and/or AFP is elevated.

E. Choriocarcinoma:

- A malignant germ cell tumor with extraembryonic differentiation.
- It is associated with increased production of human chorionic gonadotrophin (HCG), determination of urinary or plasma HCG is a useful diagnostic test.

Gross: it is typically large, unilateral, solid and hemorrhagic.

Microscopic: it is composed of malignant cyto-and syncytiotrophoblast.

Soft tissue tumors not specific to ovary:

- ☐ They include fibroma, leiomyoma, angioma, malignant lymphoma and other tumors that can arise from other tissues.
- ☐ **Fibroma** is the commonest tumor in this group. Sometimes, it reaches a large size compressing the lymphatics leading to ascites and hydrothorax (**Meig's Syndrome**).

Metastatic ovarian tumours:

1- Krukenberg tumors

- Are metastatic tumors of the ovaries.
- **Gross;** bilateral enlarged ovaries, with multinodular surface.
- **Microscopic;** signet-ring cells in a hypercellular stroma.

- The usual primary origin is from the gastro-intestinal tract or breast.
- 2- Other metastatic deposits, show a variety of patterns depending upon the site of the primary tumor.

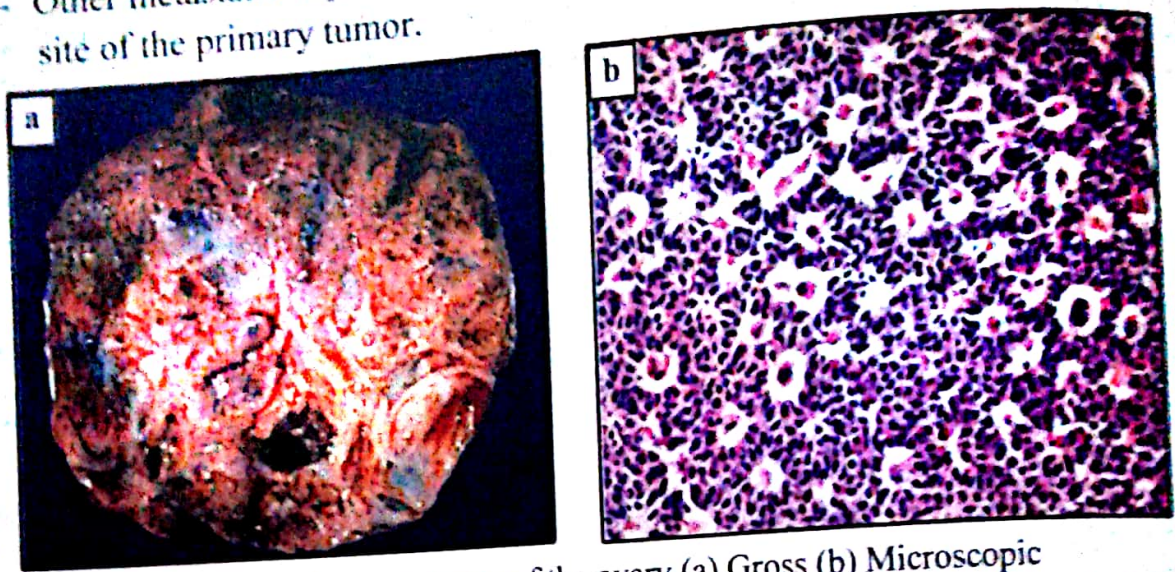


Fig.9.34: Granulosa cell tumor of the ovary (a) Gross (b) Microscopic

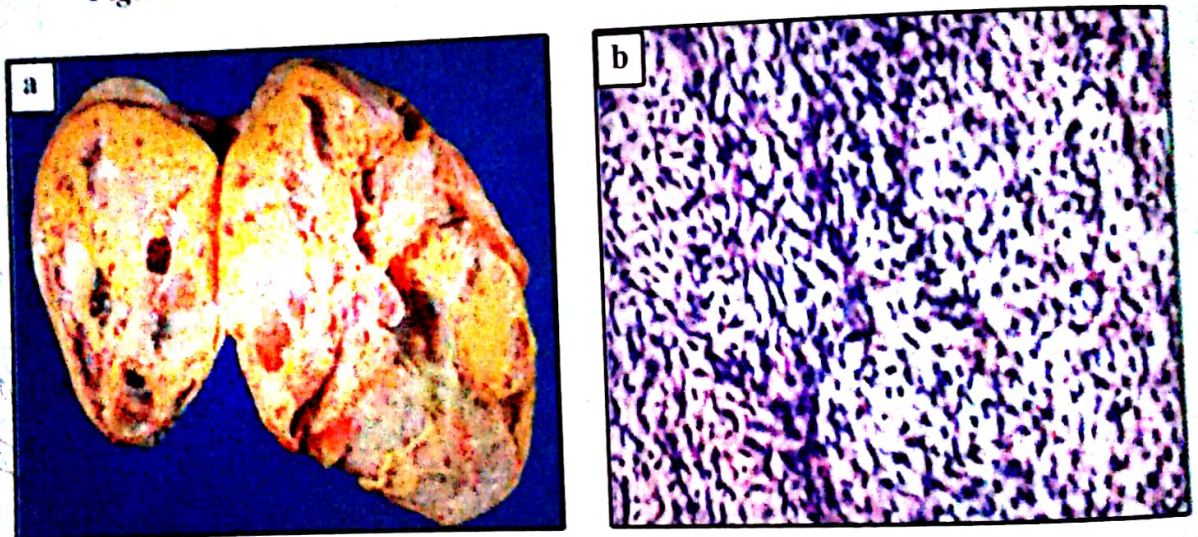


Fig.9.35: Theca cell tumor of the ovary (a) Gross (b) Microscopic

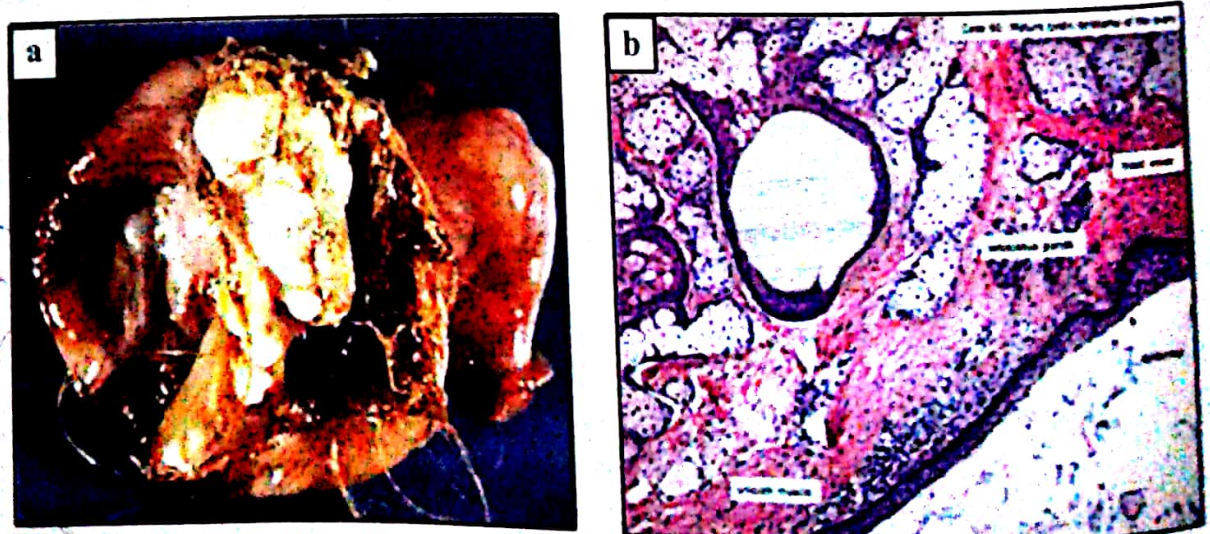


Fig.9.36: Mature cystic teratoma (a) Gross (b) Microscopic

Clinical features and complications of ovarian tumors:

1. **Asymptomatic** and discovered accidentally in 30% of ovarian tumors.
2. **Abdominal mass.**
3. **Pressure symptoms:** Particularly in large tumors as in compressing the venous drainage (leading to oedema of lower limbs), bladder or ureters (leading to obstructive urinary tract troubles).
4. **Hormonal effects:** Usually induced by functioning ovarian tumors as:
 - Granulosa theca tumors release estrogen.
 - Sertoli-leydig cell tumors release androgens.

4. Symptoms due to complications as:

- **Torsion:** in tumors with a long pedicle carrying the blood supply to the cyst wall, twisting of the pedicle might occur leading to infarction followed by gangrene. The patient presents with acute abdomen manifested by severe acute abdominal pain and hemorrhagic shock.
- **Pseudomyxomaperitonii;** it is caused by the implantation of mucinous tumor cells of borderline or malignant mucinous tumours in the peritoneum with the production of copious amount of mucin. In most cases this disorder is caused by metastasis from the gastrointestinal tract, primarily the appendix.
- **Infection:** May be acquired through blood or lymphatic or direct spread.
- **Sterility:** If bilateral and replacing most of the ovaries.
- **Malignant transformation.**
- **Meig's syndrome.**

Table.9.2: Serum tumour markers in ovarian tumours

Tumour marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Choriocarcinoma
Inhibin	Granulosa cell tumour
α -fetoprotein	Endodermal sinus tumour

SUMMARY

Non neoplastic epithelial disorders:

Lichen sclerosus, Lichen simplex chronicus.

Leukoplakia; thickened white patches of mucous membranes.

Squamous cell carcinoma of the vulva

HPV related lesions; are poorly differentiated and usually evolve from VIN.

Non-HPV-related; well differentiated and is associated with lichen sclerosis

Paget disease of the vulva: proliferation of large vacuolated malignant epithelial cells within the epidermis.

Cervical neoplasia

Risk factors; HPV exposure, early age at first intercourse, smoking,

Pathogenesis: associated with HPV (16,18). HPV express E6 and E7 proteins, which inactivate p53 and RB. In high grade dysplasia (CIN II&III); HPV is incorporated into the host genome.

Endometriosis: the presence of endometrial glands and stroma in a location outside the endomyometrium.

Adenomyosis: the growth the endometrium down into the myometrium.

Endometrial hyperplasia and endometrial carcinoma: are due to excess estrogen as failure of ovulation, estrogen producing ovarian tumours

Endometrial hyperplasia; is graded into simple, complex and atypical.

Endometrial carcinoma; endometrioid type; related to excess estrogen and endometrial hyperplasia, mutation in DNA mismatch repair genes.

Serous type; arise in endometrial polyp, mutation in P53. Aggressive, high grade.

Uterine smooth muscle tumours:

Benign leiomyomas are common and Leiomyosarcoma arise de novo.

Criteria of malignancy include; necrosis, cytologic atypia and mitoses.

Gestational trophoblastic diseases:

Complete moles, partial mole and gestational choriocarcinoma.

Ovarian tumours:

- ☐ Epithelial tumors, are serous, mucinous and endometrioid. Each may be benign, borderline or malignant.
- ☐ Sex-cord-stromal tumors: are functioning tumours, as granulosa, theca, and Sertoli-Lyedig tumours.
- ☐ Germ cell tumors: teratoma, dysgerminoma, embryonal carcinoma, endodermal sinus tumor and choriocarcinoma.

Chapter 10

Intended Learning Outcomes (ILOs)

By the end of this unit the students will be able to:

- 1. Define fibrocystic disease, explain its pathogenesis, describe the pathologic features and complications.
- 2. Compare and contrast between non-proliferative changes & proliferative changes of fibrocystic disease.
- 3. Recognize the relationship of fibrocystic changes to breast carcinoma.
- 4. Describe the pathologic features of inflammatory lesions of the breast.
- 5. Classify tumors of the breast.
- 6. Identify fibroadenoma explain its pathogenesis, pathologic and clinical features.
- 7. Describe the pathologic features and biologic behaviour of phyllodes tumor.
- 8. Describe the pathologic and clinical features and biologic behaviour of intraduct papilloma.
- 9. Classify carcinoma of the breast, list risk factors and explain its pathogenesis.
- 10. Describe the pathologic features of non-invasive duct carcinoma and state its prognosis.
- 11. Analyse and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.
- 12. Describe the pathologic features of breast lesions associated with bleeding per nipple.
- 13. Compare and contrast between ductal and lobular carcinoma in situ.
- 14. Describe the pathologic, immunophenotypic features and clinical manifestation of different invasive breast carcinomas.
- 15. Describe TNM staging system of breast cancer.
- 16. Describe the prognostic factors of breast carcinoma.
- 17. Define gynaecomastia, list its causes and describe its pathological features.

DISEASES OF THE BREAST

Fibrocystic changes:

This term is applied to a number of changes in the female breast that consist predominantly of cyst formation and fibrosis. They range from bland to patterns associated with an increased risk of breast carcinoma.

- ❑ These changes occur during the reproductive age. They are most likely a consequence of the cyclic breast changes that occur normally during the menstrual cycle.
- ❑ Estrogenic therapy and oral contraceptives do not seem to increase the incidence of these alterations; indeed, oral contraceptives may decrease the risk.

Fibrocystic changes can be subdivided into:

1- **Non proliferative changes:** In the form of *cysts and fibrosis*.

2- **Proliferative changes:** these include;

- a- Epithelial hyperplasia of breast ducts, ductules and lobules (with or without atypia)
- b- Adenosis (proliferation of terminal ducts)

Gross appearance of fibrocystic changes:

- Usually multifocal and bilateral.
- Ill-defined, diffusely increased density and discrete nodularities.
- The cysts vary from smaller than 1 cm to 5 cm in diameter. They are brown to blue (blue dome cysts) and are filled with watery turbid fluid.

Microscopic (Fig.10.1):

- 1- **Cysts** are lined by cuboidal to columnar epithelial cells that may be flattened in large cysts,
- 2- **Epithelial hyperplasia** of the lining cells may result in stratification (epitheliosis).
 - Hyperplastic epithelium may project as intraluminal papillary infolding (**papillomatosis**).
 - The degree of hyperplasia, judged in part by the number of layers of intraductal epithelial proliferation, can be mild, moderate, or severe (florid).

Chapter 10: Diseases of the breast

- Hyperplasia may be graded into atypical hyperplasia or without atypia.
- 3. **Apocrine metaplasia**: the metaplastic cells line the dilated mammary ducts appear large polygonal, with abundant granular, eosinophilic cytoplasm, and small, round, deeply stained nuclei.
- 4. The stroma surrounding the cysts is formed of compressed fibrous tissue with lymphocytic infiltrate.

Clinical presentation:

- Fibrocystic changes produce palpable lumps.
- Nipple discharge (serous or serosanguineous).

Sclerosing Adenosis

- This is an uncommon variant of fibrocystic disease.
- It is significant because its clinical and morphologic features resemble carcinoma.

Gross: Hard, rubbery masses, similar to that of breast cancer.

Microscopic: Marked stromal fibrosis, which may compress and distort the the lumina of the proliferating acini and ducts so they appear as solid cords of cells (Fig. 10.2).

Table 1: Relationship of fibrocystic changes to breast carcinoma

<i>Risk of breast carcinoma</i>	<i>Fibrocystic changes</i>
Minimal or no increased risk	- Fibrosis. - Cystic changes. - Apocrine metaplasia. - Mild hyperplasia.
Slightly increased risk (1.5-2 times)	- Moderate to florid hyperplasia (without atypia). - Ductal papillomatosis. - Sclerosing adenosis.
Significantly increased risk (5 times)	- Atypical hyperplasia (ductular or lobular).
A family history of breast cancer may increase the risk in all categories (e.g., up to 10-fold with atypical hyperplasia).	

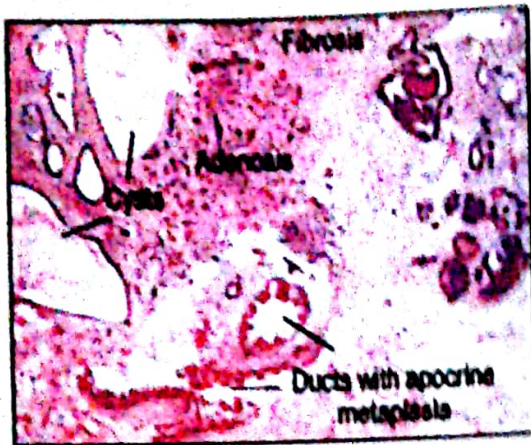


Fig.10.1: Fibrocystic changes of the breast.

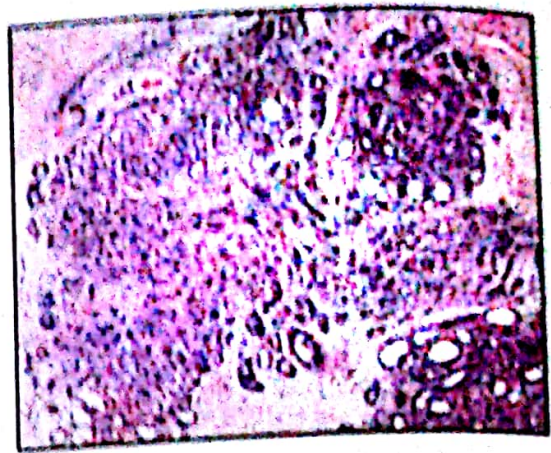


Fig.10.2: Sclerosing adenosis.

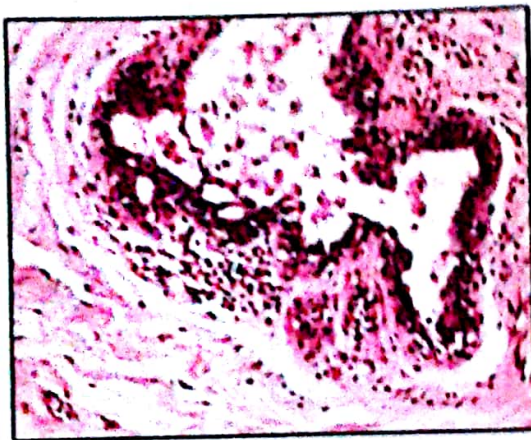


Fig.10.3: Duct ectasia.



Fig.10.4: Traumatic fat necrosis.

Inflammation:

Inflammations of the breast are uncommon and during the acute stages usually cause pain and tenderness in the involved areas.

1- Acute mastitis:

- It develops when bacteria gain access to the breast tissue through the ducts.
- The vast majority of cases arise during the early weeks of nursing when the skin of the nipples is liable to fissures.

2- Mammary duct ectasia: (periductal or plasma cell mastitis)

It is nonbacterial chronic inflammation of the breast associated with inspissation of breast secretions in the main excretory ducts.

- It is an uncommon condition, usually encountered in parous women between 45 and 60 years of age.

Microscopic (Fig. 10.3):

- The ducts are filled by granular debris, sometimes containing leukocytes and lipid-laden macrophages.
- The lining epithelium is generally destroyed.
- The most distinguishing features are the prominent lymphoplasmocytic infiltrate and the occasional granulomas in the periductal stroma.

NB: Mammary ductectasia is of principal importance because ductal dilation and rupture leads to reactive changes in the surrounding breast tissue that may present as a poorly defined periareolar mass with nipple retraction, mimicking the changes caused by some carcinomas.

3- Traumatic fat necrosis:

This lesion is significant only because it produces a mass. Most, but not all women with this condition report the occurrence of trauma to the breast.

Microscopic:

- Early it consists of a central focus of necrotic fat cells surrounded by neutrophils and lipid-laden macrophages with giant cells.
- Later it becomes enclosed by fibrous tissue and mononuclear leukocytes.
- Eventually the focus is replaced by scar tissue and calcifications may develop (**Fig. 10.4**).

Tumours of the breast

I- Benign tumors:

I- Fibroadenoma:

- ☐ It is by far the most common benign neoplasm of the female breast.
- ☐ An absolute or relative increase in estrogen activity is thought to contribute to its development.
- ☐ Fibroadenomas usually appear in young women; the peak incidence is in the third decade of life.

Pathogenesis:

The basis of ductal proliferation is not clear; perhaps the neoplastic stromal cells secrete growth factors that induce proliferation of epithelial cells. Fibroadenomas almost never become malignant.

Gross:

- Usually solitary nodule, 1 to 10 cm in diameter.

- Rarely, multiple tumors are encountered, and rarely do they exceed 10 cm in diameter (giant fibroadenoma).
- Encapsulated, firm with a uniform tan-white colour on cut section (Fig. 10.5a).

Microscopic:

It is a biphasic neoplasm formed of:

- a. Loose fibroblastic stroma
- b. Duct like, epithelium-lined spaces of various forms and sizes.
 - These duct like or glandular spaces are lined with regular luminal and myoepithelial cells with a well-defined, intact basement membrane.
 - Although in some lesions the ductal spaces are open, round to oval, and fairly regular (pericanalicular fibroadenoma "Fig. 10.5b"), others are compressed by extensive proliferation of the stroma, so that on cross-section they appear as slits or irregular star-shaped structures (intracanalicular fibroadenoma). Most cases are of mixed patterns.

Clinical picture of fibroadenomas:

- They usually present as solitary, discrete, freely movable masses.
- They may enlarge late in the menstrual cycle and during pregnancy.
- After menopause they may regress and calcify.

2- Phyllodes Tumor

- Phyllodes means "leaflike" in Greek.
- These tumors are much less common than fibroadenomas.
- They are thought to arise from the periductal stroma and not from preexisting fibroadenomas.
- They occur in old females with average age incidence of 45 years

Gross:

- Usually large but also may be small, ranging in size from 1-45cm.
- It is a solid, fleshy mass with cystic areas showing leaf-like clefts and slits (Fig. 10.6a).

Microscopic:

- Benign epithelial component and hypercellular stroma.
- It is characterized by leaf-like processes protruding into cystic spaces (Fig. 10.6b).
- Malignant changes are observed as increased stromal cellularity with anaplasia, high mitotic activity, rapid increase in size and infiltrative margins.

Biological behavior:

Most of these tumors remain localized and are cured by excision. Malignant lesions may recur, but they also tend to remain localized. Only 15% of cases metastasize to distant sites.

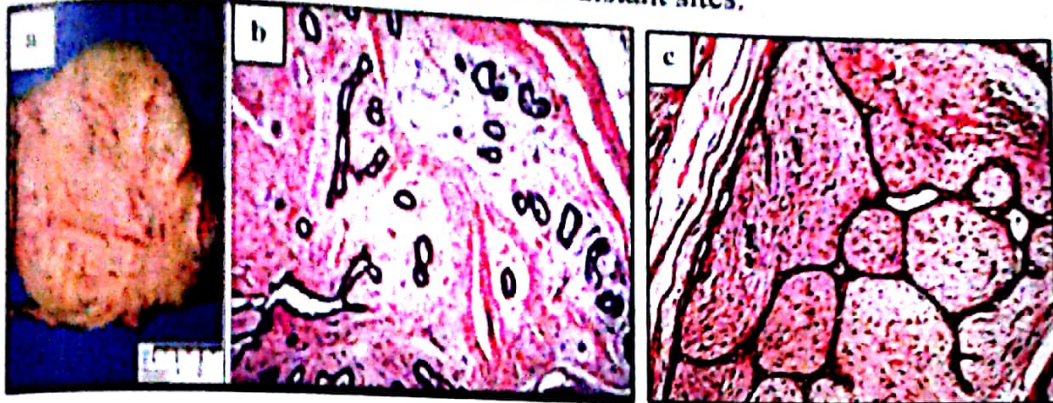


Fig.10.5: Fibroadenoma (a) Gross (b) Pericanalicular (c) Intracanalicular

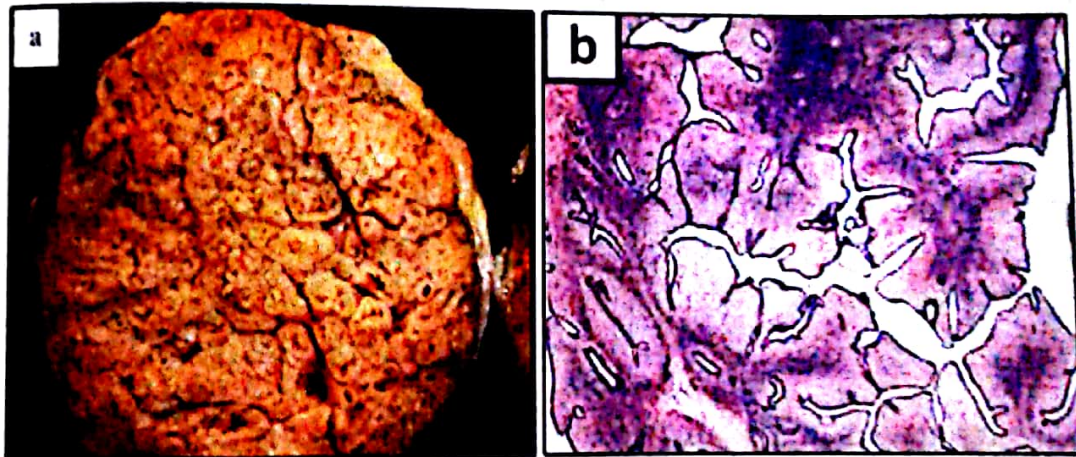


Fig.10.6: Phyllodes tumour (a) Gross (b) microscopic

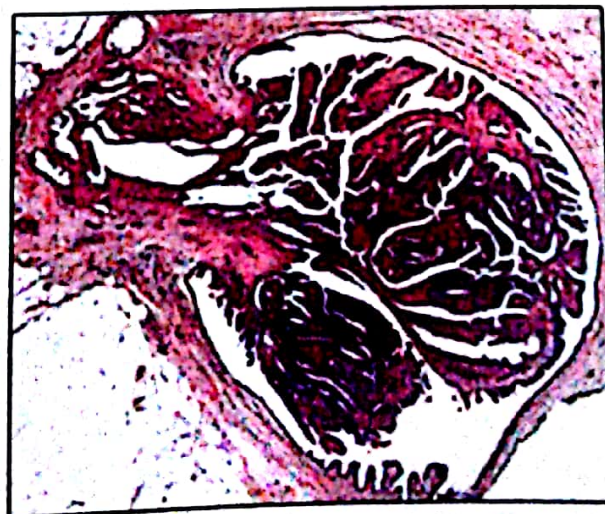


Fig.10.7: Intraduct papilloma

3- Intraductal Papilloma:

This is a benign neoplastic papillary growth within the principal lactiferous ducts.

Gross: Usually solitary and less than 1 cm in diameter.

Microscopic:

- Delicate, branching growths within dilated duct or cyst.
- These are composed of multiple papillae, each having a connective tissue core covered by double layered epithelial cells, with an outer luminal epithelial layer overlying a myoepithelial layer (Fig.10.7).

Clinical features:

1. Serous or bloody nipple discharge.
2. Small subareolar mass a few millimeters in diameter.
3. Rarely, nipple retraction.

II- Malignant tumors:

Breast carcinoma:

- ❑ It is the most common tumour in females world wise including Egypt.
- ❑ The majority of cases are above 50 years.
- ❑ 1% of breast carcinoma occurs in male.

Risk Factors

A large number of risk factors have been identified that modify a woman's likelihood of developing this form of cancer, these include:

- Geographic factors: The risk of developing breast cancer is higher in North America and Europe than in Asia and Africa.
- Age: Increases after the age of 50 years, only 5% below 40 years.
- Family history: There is 1.2-3 times increased risk in first degree relatives.
- Menstrual history: Age at menarche <12 years and age at menopause > 55 years.
- Pregnancy: Null parity and late pregnancy carries a relative risk.
- Benign breast disease: Proliferative lesion without atypia carries 1.6 fold increased risks whereas proliferative lesion with atypical hyperplasia which carries >2 fold increased risk.
- Lobular carcinoma in situ: Has 7-12 times increased risk.
- Ionizing radiation to the chest: Increases the risk for breast cancer.
- Other less established factors: Exogenous estrogens, oral contraceptives, obesity, high-fat diet, alcohol consumption and cigarette smoking.

Chapter 10: Diseases of the breast

Pathogenesis:

The cause of breast cancer remains unknown. However, the following influences seem to be important:

- 1) **Genetic changes:** Occur in both familial and sporadic settings.
 - Most likely, multiple acquired genetic alterations occur as;
 - Overexpression of *HER2/NEU* proto-oncogene which is associated with a poor prognosis.
 - About 5% -10% of breast cancers is related to specific inherited mutations in *BRCA1* gene or less commonly in *BRCA2*. Both are DNA repair genes that act as tumor suppressor genes.
- 2) **Hormonal Influences:**
 - *Endogenous estrogen* excess, or more accurately, hormonal imbalance (as in nulliparity, and late age at birth of first child) has a significant role. Functioning ovarian tumors are associated with breast cancer in postmenopausal women.
 - Estrogens stimulate the production of growth factors by normal breast epithelial cells and by cancer cells.
- 3) **Environmental variables:** Are suggested by geographic differences in prevalence. Important environmental variables include irradiation and exogenous estrogens.

The chief forms of carcinoma of the breast are classified as follows:

- a) **Noninvasive;** have not penetrated the limiting basement membrane.
 - ☐ Ductal carcinoma in situ (DCIS)
 - ☐ Lobular carcinoma in situ (LCIS)
- b) **Invasive (infiltrating);** penetrated the limiting basement membrane.
 - ☐ Invasive ductal carcinoma ("not otherwise specified")
 - ☐ Invasive lobular carcinoma
 - ☐ Medullary carcinoma
 - ☐ Colloid (mucinous) carcinoma
 - ☐ Tubular carcinoma
 - ☐ Other types

Of these, invasive ductal carcinoma is by far the most common.

A) Noninvasive (In Situ) carcinoma:

1. Ductal carcinoma in situ:

- DCIS tends to fill and distort duct spaces.
- *Microscopic patterns* are often mixed and include;

Chapter 10: Diseases of the breast

- Comedo, cribriform, solid, micropapillary, papillary, and clinging types (Fig. 10.8).
- The comedo subtype is distinctive and is characterized by cells with high-grade nuclei distending spaces with extensive central necrosis.
- Calcifications frequently are associated with DCIS.

Prognosis for DCIS

- It is excellent, with over 97% long-term survival after simple mastectomy.
- On the other hand, at least one-third of women with small foci of DCIS will eventually develop invasive carcinoma.

Paget disease of the nipple

INVASIVE CARCINOMA It is caused by the extension of DCIS up to the lactiferous ducts and into the contiguous skin of the nipple. *red nipple*

Clinical: there is usually a unilateral crusting exudate over the nipple and areolar skin.

- In about half of cases, an underlying invasive carcinoma will also be present.

Microscopic: Large clear cells with atypical nuclei are seen within the epidermis, usually along the basal layer, but also permeating the malpighian layer (Fig. 10.9).

Prognosis is based on the underlying carcinoma and is not worsened by the presence of Paget disease. *bad in case of misdiagnosis*

2- Lobular carcinoma in situ

LCIS usually expands but does not alter the underlying lobular architecture.

Microscopic:

- The cells are monomorphic with bland, round nuclei and occur in loosely cohesive clusters in the lobules (Fig. 10.10).
- Intracellular mucin vacuoles are common.
- Calcifications and necrosis are rare.

Prognosis for LCIS

- Approximately one-third of women with LCIS will eventually develop invasive carcinoma.
- LCIS also carries an increased risk of developing breast cancer in the contralateral breast.

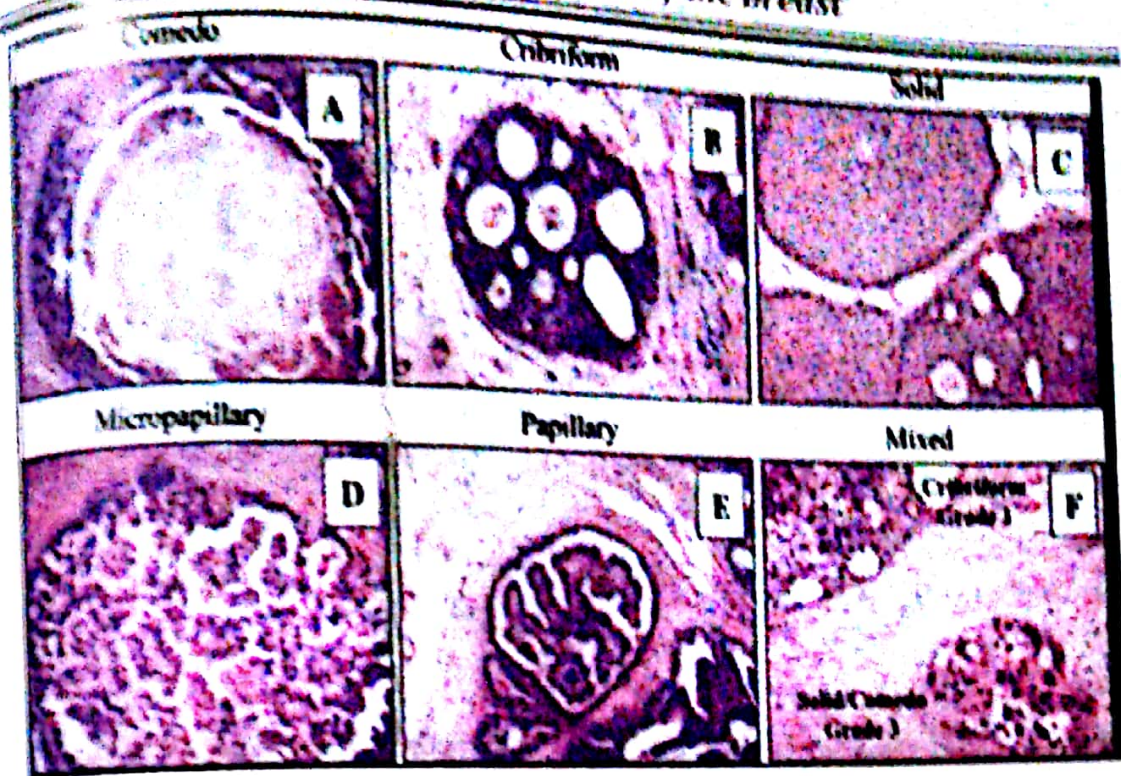


Fig.10.8: Different patterns of ductal carcinoma in situ



Fig.10.9: Paget disease of the breast

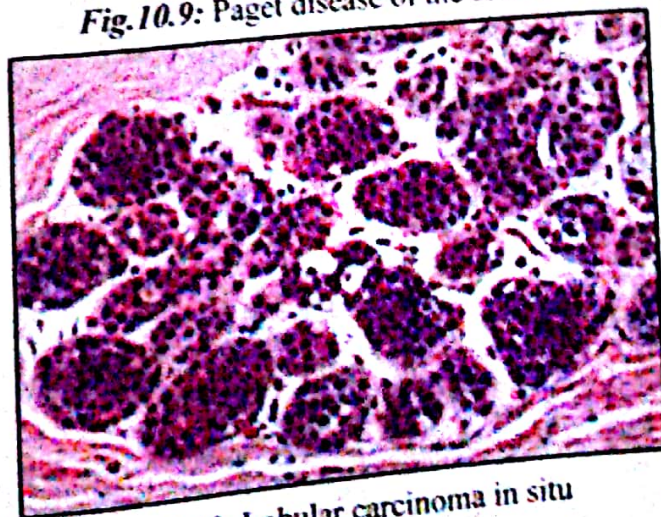


Fig.10.10: Lobular carcinoma in situ

B) Invasive (Infiltrating) carcinoma:

1- Invasive duct carcinoma:

- The majority (70% to 80%) of breast cancers fall into this group.
- This type of cancer is usually associated with DCIS, but rarely LCIS is present.
- Most duct carcinomas produce a desmoplastic reaction (resulting in mammographic densities) and form hard masses.

Gross:

- A firm poorly circumscribed mass, with gritty sensation on cutting.
- Cut surface in grayish yellow.
- The tumor infiltrates the adjacent fat in crab-like pattern, from which the word "cancer" has originated. The tumor margins are usually irregular (*Fig. 10.11a*). *no calcification*

Microscopic: It is quite heterogeneous, ranging from tumors with well-developed tubule formation and low-grade nuclei to tumors consisting of sheets of anaplastic cells (*Fig. 10.11b*).

Immunophenotype: About two-thirds express estrogen or progesterone receptors, and about one-third overexpress HER2/NEU.

2- Invasive lobular carcinoma:

Gross: Lobular carcinomas are more frequently multicentric and bilateral (10% to 20%). *irregular firm*

Microscopic:

Invasive lobular carcinoma consists of cells morphologically identical to the cells of LCIS. *small malignant cells arranged in lines*

- Two-thirds of the cases are associated with adjacent LCIS.
- The cells invade individually into stroma and are often aligned in strands or chains. Occasionally they surround cancerous or normal-appearing acini or ducts, creating a so-called bull's-eye pattern or targetoid pattern (*Fig. 10.12*).

Immunophenotype: Almost all of the cases express hormone receptors, but HER2/NEU over expression is very rare or absent. *good*

3- Inflammatory carcinoma:

- A clinical diagnosis of enlarged, erythematous and edematous breast, usually without a palpable mass.
- **Microscopic;** it is a poorly differentiated diffusely infiltrative aggressive tumour.

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- Lymphatics are so involved by tumor emboli that skin drainage is blocked, causing lymphedema and thickening of skin of majority of breast (**Pseudorange** "orange peel").

4- Medullary carcinoma:

It is a rare subtype of carcinoma constituting less than 1% of cases.

Pathological features: *well defined, soft*

- The tumour consists of sheets of large anaplastic cells.
- Have well-circumscribed pushing tumor borders (**Fig.10.13**).
- There is a pronounced lymphoplasmocytic infiltrate.
- DCIS is usually absent or minimal.
- Occurs frequently in women with BRACA-1 mutation.

Immunophenotype: These carcinomas uniformly lack hormone receptors and do not overexpress HER2/NEU. *Relatively good*

5- Colloid (mucinous) carcinoma:

It is a rare subtype that often presents as well-circumscribed mass.

Gross: Tumors are usually soft and gelatinous (**Fig.10.14**).

Microscopic: Tumor cells produce abundant quantities of extracellular mucin that dissect into the surrounding stroma (**Fig.10.15**).

Immunophenotype: Most express hormone receptors and rare examples may overexpress HER2/NEU. *Relatively good*

6- Tubular carcinoma:

- Account for 10% of invasive carcinomas.
- Usually smaller than 1 cm, found with mammographic screening.

Microscopic: Consists of well-formed tubules with low-grade nuclei (**Fig.10.16**).

Immunophenotype: Virtually all tubular carcinomas express hormone receptors, but over expression of HER2/NEU is highly unusual. *good*

Clinical features of breast carcinomas:

- Usually present as painless palpable masses or mammographic densities, but some may be clinically occult.
- Advanced cancers may cause dimpling of the skin, retraction of the nipple, or fixation to the chest wall.
- Involvement of the lymphatic pathways may cause localized lymphedema.

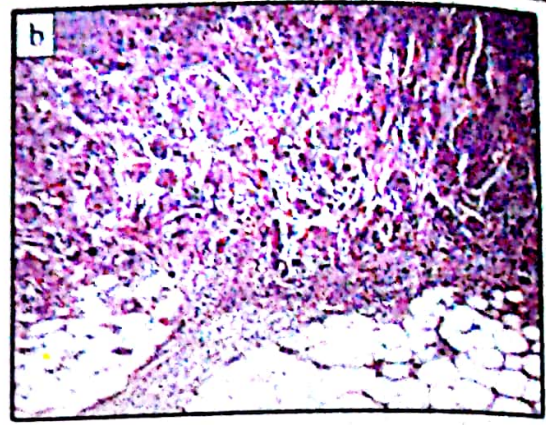


Fig.10.11; Invasive duct carcinoma (a) gross, (b) microscopic

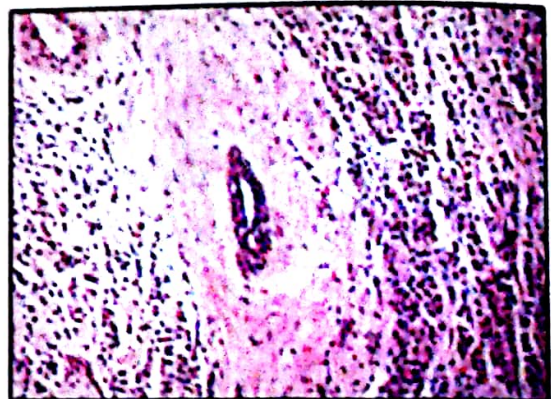
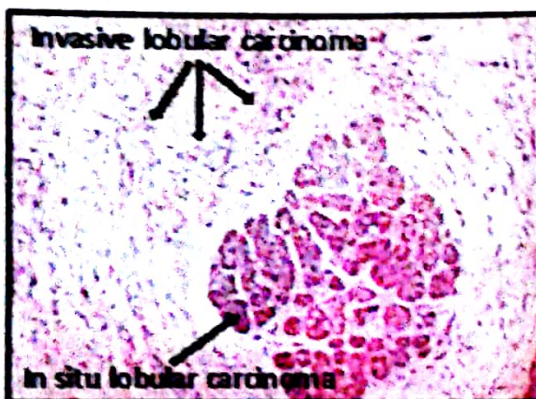


Fig.10.12; Invasive lobular carcinoma: note right targetoid growth

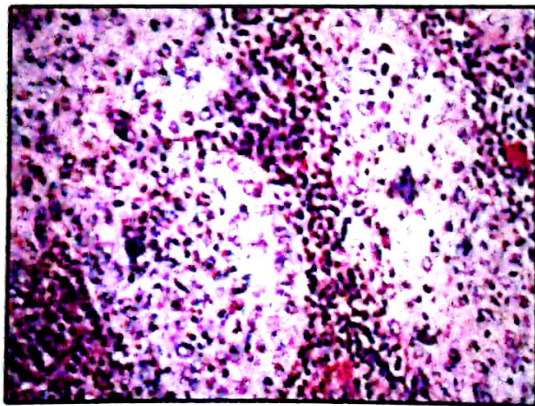


Fig.10.13; Medullary carcinoma



Fig.10.14; Mucinous carcinoma (gross)

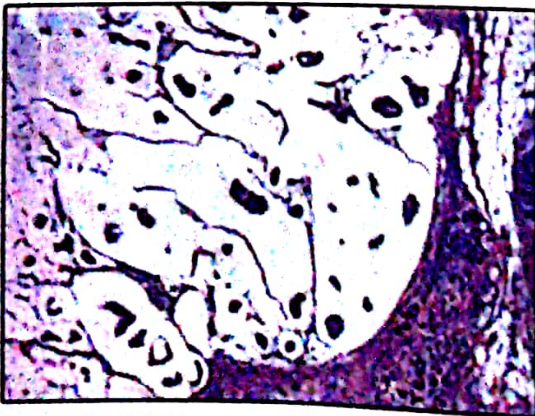


Fig.10.15; Mucinous carcinoma (microscopic)

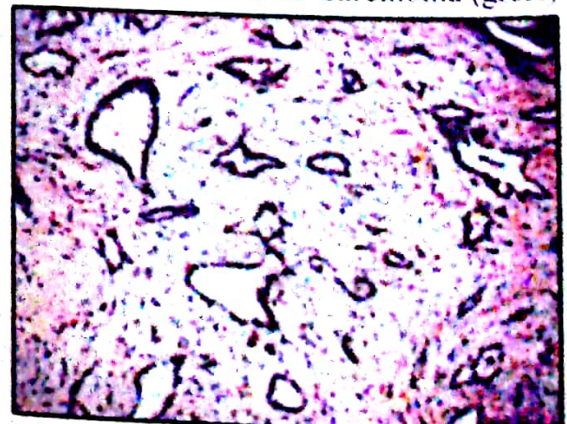


Fig.10.16; Tubular carcinoma

Spread of breast cancer:

Spread occurs through lymphatic and hematogenous channels.

○ Lymph node metastases:

- At the time of clinical detection of breast cancer (mass of 2-3cm) 50% of cases have lymph node metastasis.
- Nodes affected are;

The axillary nodes in **outer quadrant tumours** ✓

The internal mammary nodes in medial (inner) quadrant tumours.

- Distant hematogenous spread: To the lungs, skeleton, liver, and adrenals. Less commonly to the brain, spleen, and pituitary.
- Metastasis may occur many years after apparent therapeutic control. Nevertheless, with each passing year without tumour recurrence the likelihood of cure increases.

Prognostic factors of breast cancer:

Prognosis is influenced by the following variables (note that the first three are components of tumor "TNM" staging system):

1. Invasion and the size of the primary carcinoma. CIS and tumours smaller than 1 cm have excellent prognoses.
2. Lymph node metastasis and the number of lymph nodes involved. With no axillary node involvement, the 5-year survival rate is close to 90%. The survival rate decreases with each involved lymph node and is less than 50% with 16 or more involved nodes.
3. Distant metastases. Patients who develop hematogenous spread are rarely curable, although chemotherapy may prolong survival.
4. Histologic grade. The common grading system for breast cancer evaluates tubule formation, nuclear grade, and mitotic rate to divide carcinomas into three groups. Well-differentiated carcinomas have a significantly better prognosis as compared with poorly differentiated carcinomas.
5. The histologic type of carcinoma. All specialized types of breast carcinoma (tubular, medullary, cribriform, adenoid cystic, and mucinous) have a somewhat better prognosis than ductal carcinomas of no special, except inflammatory carcinoma which has a poor prognosis.
6. The presence or absence of estrogen or progesterone receptors: The presence of hormone receptors confers a slightly better prognosis. However, the reason for determining their presence is to predict the response to therapy.

7. The proliferative rate of the cancer. Proliferation can be measured by mitotic counts, flow cytometry, or immunohistochemical markers for cell cycle proteins as Ki67. High proliferative rates are associated with a poorer prognosis.
8. Overexpression of HER2/NEU:
- It is caused by amplification of the gene.
 - Associated with aggressive tumours.
 - The importance of evaluating HER2/NEU is to predict the tumour response to "Herceptin" therapy.

Lesions of the male breast

The male breast is relatively free of pathologic involvement. Only two disorders occur with sufficient frequency to be considered here:

Gynecomastia:

Gynecomastia is enlargement of the male breast.

It may occur in response to absolute or relative estrogen excesses as in:

- Cirrhosis of the liver, with consequent inability of the liver to metabolize estrogens.
- Other causes include Kline felter syndrome, estrogen-secreting tumors, estrogen therapy and occasionally digitalis therapy.
- Physiologic gynecomastia often occurs at puberty and in old age.

Gross: a button-like, subareolar swelling develops, usually in both breasts but occasionally in only one.

Microscopic: the ducts show prominent epithelial hyperplasia surrounded by a hyalinized stroma.

Carcinoma of the male breast:

- ❑ It is rare, with a male/female ratio of 1: 125.
- ❑ It occurs in advanced age.
- ❑ Because of the scant amount of breast substance in the male, the tumor rapidly infiltrates the overlying skin and underlying thoracic wall.
- ❑ Both morphologically and biologically, these tumors resemble invasive carcinomas in the female.
- ❑ Unfortunately, almost half have spread to regional nodes and more distant sites by the time they are discovered.

SUMMARY

Fibrocystic changes:

- Non proliferative changes (cysts and fibrosis).
- Proliferative changes (Epithelial hyperplasia with or without atypia and adenosis), sclerosing adenosis.
- Relationship of fibrocystic changes to breast carcinoma: Atypical hyperplasia is associated with a five-fold increase in the risk of developing carcinoma; when associated with a family history of breast carcinoma, the risk is 10-fold.

Inflammation:

Acute mastitis.

Mammary duct ectasia: It is nonbacterial chronic inflammation of the breast associated with inspissation of breast secretion in the main excretory ducts

Traumatic fat necrosis.

Tumours of the breast: Fibroadenoma, phyllodes tumor, intraductal papilloma

Breast carcinoma:

Risk Factors: Geographic factors, age, family history, menstrual history, age at menarche, pregnancy, benign breast disease, lobular carcinoma in situ, ionizing radiation to the chest.

Pathogenesis: Genetic, hormonal & environmental variables.

Type: Noninvasive; DCIS & LCIS.

- Invasive ductal, lobular, inflammatory, medullary, colloid & tubular carcinoma.

Spread of breast cancer: Direct, lymph node & blood spread.

Prognosis:

- The size of the primary carcinoma.
- Lymph node metastasis and the number of lymph nodes involved.
- Distant metastases.
- The grade of the carcinoma.
- Histologic type of carcinoma.
- The presence or absence of estrogen or progesterone receptors.
- The proliferative rate of the cancer.
- Overexpression of HER2/NEU.

Chapter 11

Intended Learning Outcomes (ILOs)

By the end of this unit the students will be able to:

- 1. Define thyroiditis and describe the pathologic features of Hashimoto's thyroiditis.
- 2. Define goiter, list types of simple goiter, explain pathogenesis and describe its pathologic features.
- 3. Identify Graves' disease, explain pathogenesis and describe the pathologic features.
- 4. Enumerate causes and clinical features of hypothyroidism.
- 5. Classify tumours of the thyroid gland, recognize the predisposing factors and describe the pathologic features of papillary carcinoma.
- 6. Identify cell of origin of malignant thyroid tumours and its relation to clinical features of medullary carcinoma.
- 7. Compare between primary and secondary hyperparathyroidism.
- 8. Classify tumours of adrenal cortex, describe the pathologic features of neuroblastoma.
- 9. List causes and clinical features of adrenal cortical insufficiency.
- 10. Describe the pathological features of pheochromocytoma.
- 11. Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and / or laboratory findings.
- 12. Enumerate types of pituitary adenomas, describe the pathologic features and clinical manifestation of each type.
- 13. Classify thymoma and describe the pathologic features.
- 14. Define multiple endocrine neoplasia syndromes and their distinctive features.

CNS

nerve injury

missile wounds → chromatolysis

necrosis → Red neuron

spherical → swelling of the axon

astrocytes

periplex → sympathetic

cellular → cellular

ENDOCRINE GLANDS

Diseases of the thyroid gland:

Thyroiditis:

It is inflammation of thyroid gland.

A) Infectious thyroiditis:

- The causative agents include **staph. aureus**, **streptococci** and **fungi**.
- The infection is **haematogenous**, leading to **enlarged tender gland**.
- **Suppuration** may develop with **abscess formation**.

B) Riedel's fibrosing thyroiditis:

- A rare, **chronic inflammatory disease** of the thyroid gland of **unknown cause** characterized by **replacement of thyroid acini by dense fibrous tissue** penetrating the capsule and **extending into the adjacent neck structures**. **Foci of lymphocytes and plasma cells are seen**.
- Manifestations include **hypothyroidism**, and **symptoms of adhesions to the surrounding tissues** e.g. trachea and recurrent laryngeal nerve.

C) Hashimoto's thyroiditis:

It is an **autoimmune inflammatory disorder** characterized by **gradual thyroid failure** and it is the **most common cause of hypothyroidism**.

It is **common in females** between 45-65 years, with female to male ratio of more than 10:1.

Pathogenesis:

- **It is an auto immune disease**, caused by a **breakdown of self-tolerance**. So circulating **auto-antibodies to thyroid antigens** are present. The immune mechanisms that may contribute to thyroid damage include:
 - **CD8+ cytotoxic T cell-mediated cell death**.
 - **Cytokine-mediated cell death**; **excessive helper T lymphocyte activation** leads to release of **interferon- γ** with resultant recruitment and **activation of macrophages** and damage of follicles.
 - **Binding of antithyroid antibodies** followed by **antibody-dependant cell-mediated cytotoxicity**.
- **Genetic factors**: include **defects in multiple immune regulation-associated genes that negatively regulate T cell function (Fig.11.1)**.

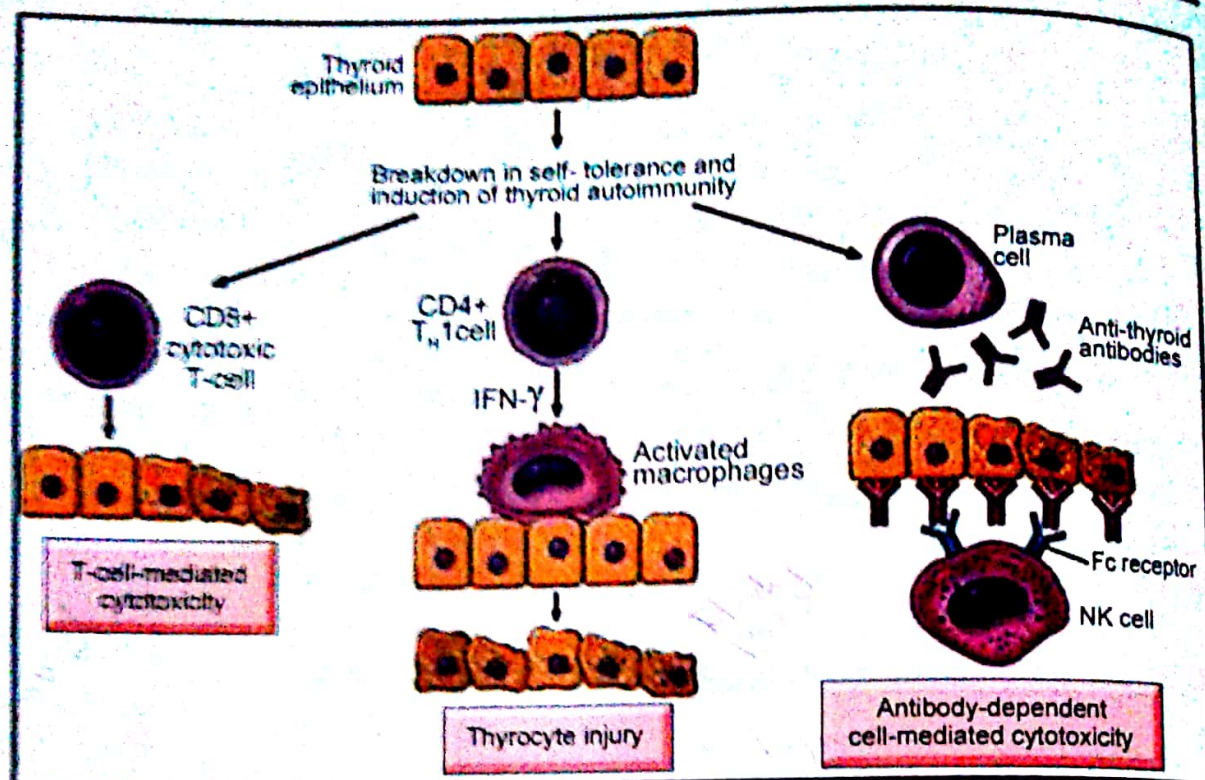


Fig.11.1: Pathogenesis of Hashimoto thyroiditis.

Gross: The gland is diffusely and symmetrically enlarged, although localized enlargement may be seen. The cut surface is fleshy, pale with grey-tan.

Microscopic (Fig.11.3):

- Diffuse infiltration of the parenchyma by lymphocytes and plasma cells with lymphoid follicles showing germinal centres!
- Atrophy of follicles with diminished amount of colloid.
- Hürthleor "Askanazy" cell metaplasia, the follicles become lined by metaplastic large cells with intensely eosinophilic, granular cytoplasm.
- Less commonly the thyroid is small and atrophic as a result of extensive fibrosis and less inflammation (Fibrosing variant).

Clinical course:

- ❑ Characterized by hypothyroidism, usually associated with painless enlargement of the gland.
- ❑ Thyromegaly is absent in atrophic (fibrosing variant).
- ❑ Hyperthyroidism (Hashitoxicosis) may be seen early but is transient.

D. Subacute granulomatous (De Quervain's) Thyroiditis:

- A self limited disease, also referred to as giant cell thyroiditis, of unknown aetiology, but viral infection may be implicated.
- The gland is enlarged, tender, and infiltrated by chronic inflammatory cells with many foreign-body giant cells.

E. Subacute lymphocytic thyroiditis:

- Uncommon cause of **painless mild enlargement of the thyroid**, with **initial phase of thyrotoxicosis**, followed by **euthyroid state** within few months.
- Most likely of **autoimmune aetiology**.
- **Microscopic:** Infiltration of thyroid parenchyma by lymphocytes with **germinal center formation**.

Goiter:

It is non-inflammatory, non-neoplastic enlargement of the thyroid gland.

- The term goiter is used to denote any enlargement of the thyroid gland.
- Goiters may be: simple or toxic, diffuse or nodular.

A- Simple goiter:

- The **gland is enlarged** but there is **no manifestations of thyrotoxicosis**, it occurs in endemic and sporadic forms.
- **Decreased production of thyroid hormone** produces a **compensatory increase in TSH** with resultant **hyperplasia and hypertrophy of the gland**.
- **Endemic goiter:**
 - It is most prevalent in areas with **dietary iodine deficiency**.
- **Sporadic goiter:** is common in **females** with a peak incidence at puberty or young adult life. It is due to:
 - **Increased physiological demands for thyroid hormones** or
 - **Hereditary enzymatic defect** that **interfere with thyroid hormone synthesis**.

Simple goiter stages:

a. Diffuse parenchymatous goiter:

Occurs early in the disease when **iodine supply is inadequate**.

Gross: Diffuse enlargement of the gland.

Microscopic: Hyperplasia of thyroid follicles and their epithelial lining cell.

b. Diffuse colloid goiter: Occurs when **iodine supply becomes adequate**.

Gross: Diffuse enlargement of the gland with brown cystic gelatinous cut, surface (colloid).

Microscopic: The follicles are distended with colloid and lined by flattened epithelium.

c. Multinodular goiter: Occurs after repeated cycles of hyperplasia and involution.

Gross:

- Nodular enlargement of the gland which is firm in consistency.
- Cut surface shows multiple nodules separated by fibrous tissue septae.
- Areas of haemorrhage, necrosis, cystic degeneration and calcification may be seen (Fig.11.4).

Microscopic:

- Multiple nodules of thyroid follicles of variable size and shape, many of them are filled with colloid.
- These nodules are separated by fibrous tissue stroma with numerous lymphocytes (Fig.11.5).

Effects of simple goiter:

1. **Pressure effects:**
 - On the trachea leading to dyspnea.
 - On the oesophagus causing dysphagia.
 - On large vessels of the neck causing superior vena cava syndrome.
2. Toxicity resulting in secondary toxic goiter.
3. Malignancy arising in longstanding multinodular goiters is low.

B- Toxic goiter:

Definition: Goiter associated with thyrotoxicosis.

Types

1. Primary toxic goiter: (Graves' disease, exophthalmic goiter).
2. Secondary toxic goiter: (toxic nodular goiter) complicating simple nodular goiter.

1- Graves' disease: (primary toxic goiter)

It is the most common cause of endogenous hyperthyroidism characterized by:

- Thyrotoxicosis.

- Infiltrative ophthalmopathy with resultant exophthalmos.
- Localized infiltrative dermopathy (pretibial myxedema).

It is common in females between the ages of 20-40 years.

Pathogenesis:

- It is an autoimmune disease, caused by a breakdown of self tolerance to thyroid auto-antigens mainly TSH receptor, resulting in the production of multiple autoantibodies including:
 - Thyroid stimulating immunoglobulins (TSI); increase the release of thyroid hormones.

- Thyroid growth stimulating immunoglobulins (TGI) cause proliferation of follicular epithelium.
- TSH-binding inhibitor immunoglobulins (TBI).
- T cell-mediated autoimmune reaction is also involved in the development of infiltrative ophthalmopathy.

Manifestations:

- a. Symptoms of thyrotoxicosis as
 - Increased basal metabolic rate "BMR".
 - Cardiovascular manifestations as palpitation, tachycardia and heart failure in severe cases.
 - Nervousness irritability, tremors and insomnia.
 - Gastrointestinal manifestations in the form of increased appetite with weight loss, malabsorption and diarrhea.
 - Excessive sweating with wet skin.
 - Sympathetic overstimulation produces to staring gaze and lid lag.
- b. Exophthalmos or eye protrusion, due to infiltration of retro-orbital tissue by oedema, fat cells and lymphocytes mostly T-cell, and accumulation of extracellular matrix.
- c. Dermatopathy (scaly thickening and induration of the skin of chins).
- d. Laboratory findings include increase in serum free T3 and T4 and decreased TSH.

Gross: Thyroid gland is diffusely (usually symmetrically) enlarged, smooth and soft with intact capsule.

Microscopic:

- There is marked epithelial hyperplasia, the cells are columnar and appear in more than one layer of cells with many small papillae.
- The follicles show little pale colloid with scalloped margins.
- The stroma shows increased vascularity and marked lymphocytic infiltration including lymphoid follicles.

2- Secondary Toxic Goiter:

It is a complication of simple nodular goiter with secondary hyperplasia especially in patients treated with iodine.

Gross: Thyroid gland is enlarged and nodular.

Microscopic:

- There are nodules of thyroid tissue, where thyroid follicles are lined by columnar epithelial cells and filled with colloid, showing scalloping at the periphery.
- Hyperplasia of the epithelium lining the follicles with papillae formation are also seen.

Hypothyroidism

1. Cretinism:

It refers to hypothyroidism developing during fetal life and early childhood.

Lesions: At first the thyroid shows compensatory hyperplasia but later, on it is replaced by fibrous tissue.

Clinical:

- Physical and mental retardation.
- Body is short and head is large.
- Enlarged protruding tongue.
- Arms are short and curved.
- Delayed ossification and underdeveloped sex organs.

2. Myxoedema:

It refers to hypothyroidism developing in older children and in adults.

It is common in females over 40 years.

Causes:

- a. Surgical removal of thyroid gland and thyroiditis/ especially Hashimoto's disease.
- b. Deficiency of TSH (pituitary myxoedema) as in tumours of the pituitary gland.

Clinical:

- Low BMR
- Dry and rough skin, thick tongue and face puffiness.
- Enlargement of the heart, increased incidence of atherosclerosis and hypercholesterolaemia.

NB: Autoimmune thyroid diseases include:

- Hashimoto's disease.
- Subacute lymphocytic thyroiditis.
- Graves's disease.

Tumours of the thyroid gland:

I- Benign tumours:

Adenomas:

They are benign neoplasms arising from follicular epithelium.

Gross: Thyroid adenoma is a rounded or oval firm solitary nodule, having a well developed capsule and a translucent brown cut surface.

Microscopic:

1. Follicular adenoma:

- It is surrounded by an intact well formed capsule.
- It is composed of well differentiated follicles containing colloid and resembles more or less normal thyroid tissue.
- Micro or macrofollicles, focal nuclear pleomorphism and atypia may be noted (Fig.11.6).

2. Hürthle cell adenoma "Oncocytic adenoma": In which most of the cells are large with granular acidophilic cytoplasm and a large vesicular nucleus.

Clinical features and effects of adenomas:

1. Most adenomas present as painless cold nodules.
2. Toxic manifestations may develop.
3. Large adenomas cause pressure symptoms as dysphagia.

II- Malignant tumours:

Almost all are carcinomas.

Types of thyroid carcinoma:

1. Papillary carcinoma:

- It is the most common form of thyroid cancer (85%).
- Occurring more in females at any age.
- Most cases are associated with previous exposure to ionizing radiation.

Gross:

- The tumour may manifest as solitary or multifocal lesions.
- It may be encapsulated, but usually unencapsulated and infiltrative.
- Small lesions less than one cm. is called microcarcinoma.
- The cut surface is granular or papillary (Fig.11.7a). It may show areas of fibrosis, calcification or cystic changes.

Microscopic:

- Papillary pattern, composed of complex papillary architecture; the malignant cells are arranged in one or more layers around fibrovascular cores (Fig.11.7b).
- Follicular variant of papillary carcinoma; the tumour is composed predominantly of follicles.
- Psammoma bodies are common.

- **The diagnostic nuclear features are:**
 - Optically clear nuclei devoid of nucleoli (ground glass nuclei).
 - Nuclear grooves.
 - Intranuclear cytoplasmic inclusions.

Spread:

- Local infiltration to surrounding tissues.
- Lymphatic spread: Common and early to cervical lymph nodes.
- Blood spread: Rare and late to the lung and bone.

2. Follicular carcinoma:

It is common in females between 40 and 60 years of age.

Etiology:

- ❑ Increased prevalence noted in areas of dietary iodine deficiency, suggests that multinodular goiter may predispose to follicular carcinoma.
- ❑ Some cases may arise in a preexisting follicular adenoma.

Gross: The tumour is fleshy, usually infiltrating the thyroid and surrounding tissues or less commonly sharply demarcated.

Microscopic:

- Most cases are well differentiated, being composed of fairly uniform cells forming small follicle reminiscent normal follicles. Less differentiated tumours show sheets of follicular cells with nuclear pleomorphism and mitotic figures.
- Tumours may be widely invasive, infiltrating the surrounding tissues or small minimally invasive.
- Capsular and/or vascular invasion are mandatory to confirm the diagnosis.

Spread:

1. Local infiltration to surrounding tissue.
2. Blood spread: Common and early, mainly to lungs and bones.
3. Lymphatic spread: Rare and late.

3. Anaplastic carcinoma:

- Rare and occurs more in elderly females above 65 years.
- Rapidly progressive neck swelling causing compression of airways.

Microscopic variants include:

- Large pleomorphic giant cells.
- Spindle cells with a sarcomatoid appearance.
- Mixed spindle and giant cell lesions.



Fig.11.3: Hashimoto thyroiditis.



Fig.11.4: Multinodular goiter.

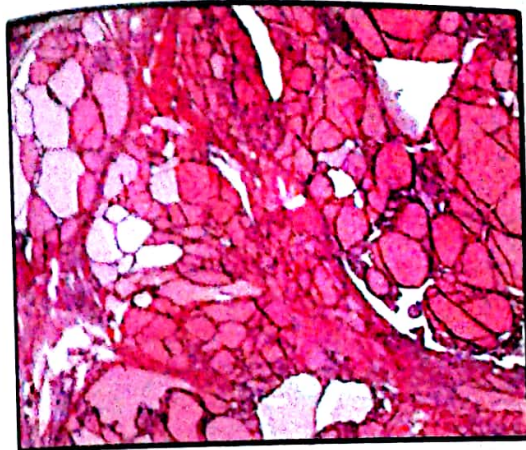


Fig.11.5: Multinodular goiter.

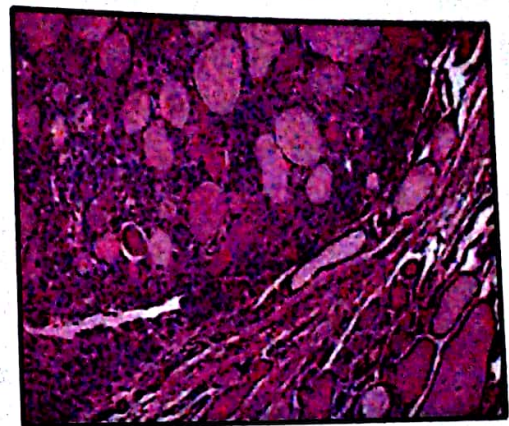


Fig.11.6: Follicular adenoma.

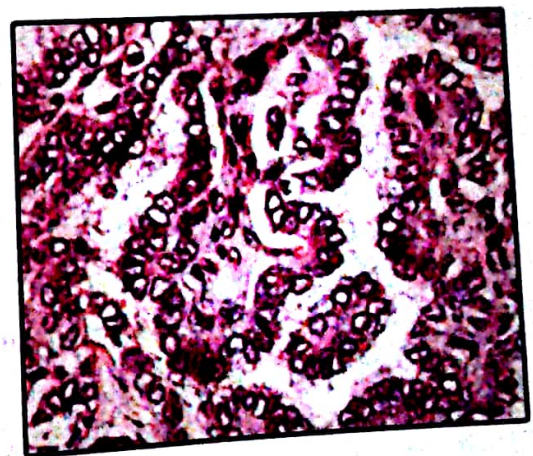
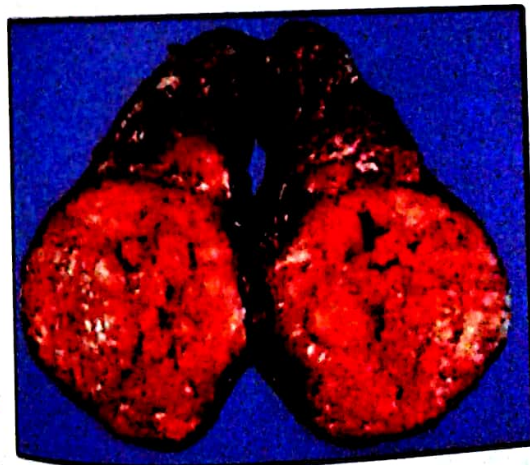


Fig.11.7: Thyroid; papillary carcinoma (a) gross, (b) microscopic.

4. **Medullary thyroid carcinoma (C-cell tumour):**

- ❑ It is a neuroendocrine neoplasm derived from parafollicular (C) cells, in contrast to other thyroid carcinomas (arise from follicular cells).
- ❑ Distinctive features include secretion of calcitonin and amyloid stroma in many cases.
- ❑ Most cases arise sporadically, but familial cases occur. When it

coexists with tumours of the parathyroid gland and adrenal glands medulla (pheochromocytoma) it is called multiple endocrine neoplasia type 2 (MEN2).

Gross: It may be a solitary or multiple nodules in both lobes with areas of hemorrhages and necrosis.

Microscopic features:

- Composed of polygonal to spindle-shaped cells arranged in organoid nests, trabeculae and occasionally follicles.
- Amyloid deposits derived from altered calcitonin molecules.
- Foci of C cell hyperplasia

Clinical:

- Neck swelling with pressure symptoms.
- Familial cases may show symptoms of hormone production.

Diseases of parathyroid glands

1. Hyperparathyroidism

It may be primary or secondary.

A- Primary hyperparathyroidism:

An important cause of high blood calcium.

Causes:

1. Primary hyperplasia occurs in 5-10% of cases, in which the 4 glands are enlarged in size.
2. Tumours such as:
 - a. Adenoma: Occurs in 85-90% of cases of hyperparathyroidism and affects one gland only. The gland is enlarged orange brown and becomes embedded in the thyroid tissue.
 - b. Carcinoma of parathyroid (in 1% of cases).

Morphological changes in other organs (Fig.11.8):

1. Skeletal lesions:

- Decalcification with generalized osteoporosis.
 - Diffuse osteitis fibrosa cystica (brown tumour) in severe cases.
2. Metastatic calcification resulting in urinary stones and nephrocalcinosis (calcification of renal interstitium and tubules).

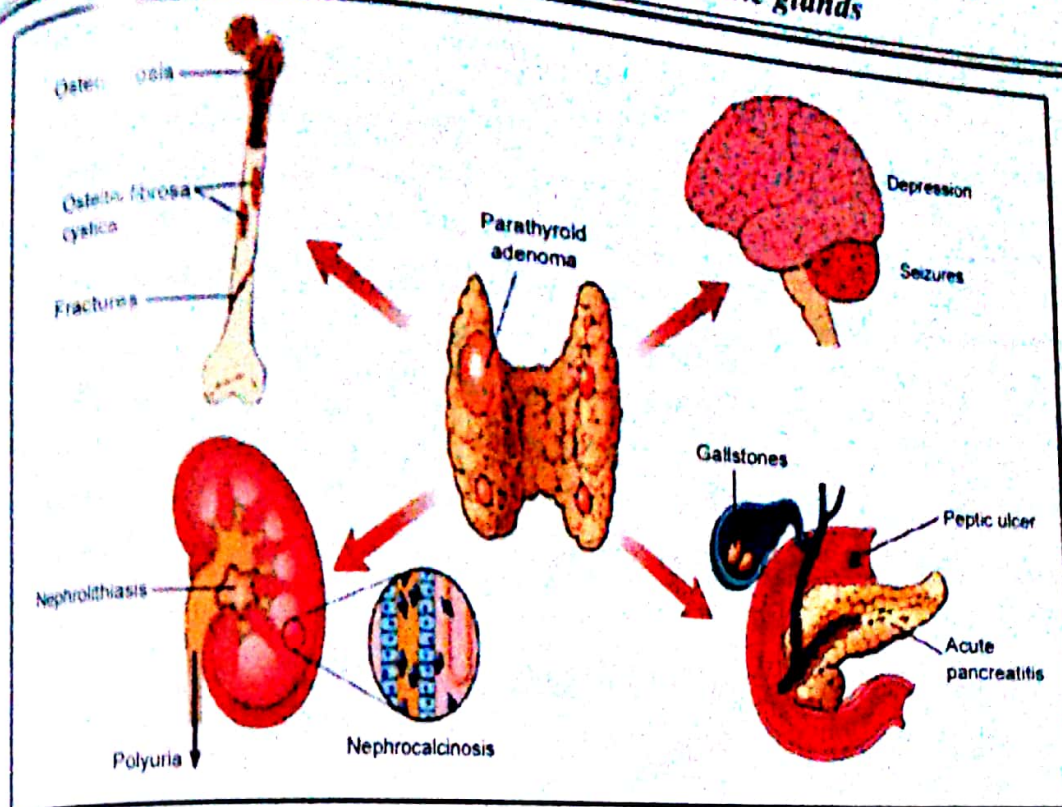


Fig.11.8; Cardinal features of hyperparathyroidism.

B-Secondary hyperparathyroidism:

It is due to **compensatory hyperplasia** of the parathyroids in conditions with **low blood calcium**. *confirmed by sonography.*

Causes:

Chronic renal insufficiency is associated with **decreased excretion of phosphorus** leading **hyperphosphatemia**, the latter directly depress the **calcium levels** and thereby **stimulate parathyroid gland activity**.

II. Hypoparathyroidism:

- ❑ It is due to hypoplasia of the glands or due to **surgical removal** e.g. during neck surgery or thyroidectomy.
- ❑ The **serum calcium is low** and the blood phosphorus is either normal or raised.
- ❑ Hypoparathyroidism results in **tetany**.

Diseases of the suprarenal gland

- The adrenal glands are paired endocrine organs consisting of both cortex and medulla. The cortex is formed of three layers of distinct cell types; zona glomerulosa, Zona reticularis and zona fasciculata.
- The adrenal cortex synthesizes three different types of steroids:
 - 1) Glucocorticoids (principally cortisol)
 - 2) Mineralocorticoids, the most important being aldosterone.
 - 3) Sex steroids (estrogens and androgens).
- The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines, mainly epinephrine.

(A) Adrenal cortex:

I. Hyperfunction of adrenal cortex:

The results depend on the type of cell affected and hormone produced.

Cushing's syndrome:

Due to excess glucocorticoids

Causes:

1- Endogenous:

- Basophil adenoma of the anterior pituitary. In 70% of Cushing's syndrome, the pituitary gland contains an ACTH-producing micro-adenoma that does not produce mass effects in the brain.
- Primary hyperplasia or a tumor of adrenal cortex whether (adenoma or carcinoma),
- Secretion of ectopic ACTH by non- endocrine neoplasms; as small-cell carcinoma of the lung, rarely by carcinoid tumors, medullary carcinomas of the thyroid, and islet cell tumors of the pancreas.

2- Exogenous: prolonged intake of cortisone.

Morphology: The adrenals have one of the following abnormalities:

- Cortical atrophy in cases of exogenous glucocorticoids,
- Diffuse hyperplasia found in 60% to 70% of cases of endogenous Cushing syndrome (ACTH-dependent hyperplasia).
- Nodular hyperplasia in adrenal Cushing's.
- The adrenocortical adenomas are yellow tumors surrounded by thin capsules and most weigh less than 30 gm. They are composed of cells that are similar to those encountered in the normal zona fasciculata.

- This disorder is about four times higher in women than men.
 It occurs most frequently during young adulthood (20-30 years).
 Obesity, moon face, muscle weakness, DM, impotence, menstrual disorders and hypertension

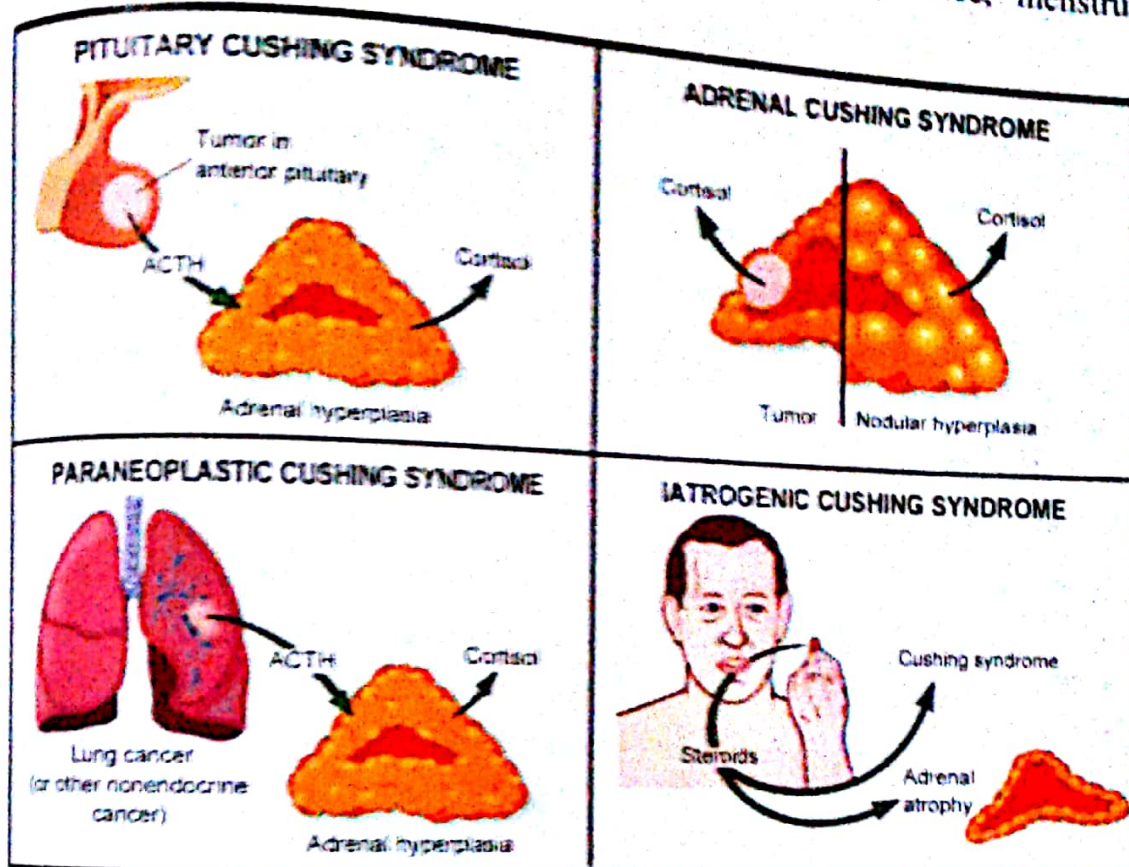


Fig.11.9: Morphology of adrenal gland in Cushing's syndrome.

Conn's syndrome:

It is primary hyperaldosteronism due to aldosterone-secreting adenoma.

Gross:

- Aldosterone secreting **adenomas** are mostly solitary, small, encapsulated yellow lesions.
- They do not usually suppress ACTH secretion therefore; the adjacent adrenal cortex and that of the contralateral gland are not atrophic.

Microscopic:

- The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid and characteristically contain **eosinophilic laminated cytoplasmic inclusions, known as spironolactone bodies**.

Clinical: Hypertension, hypokalemia, muscle weakness, polyuria and albuminuria.

Adrenogenital syndrome:

- Excess androgen may be caused by either primary gonadal disorder or primary adrenal disorder.
- Unlike gonadal androgens, adrenal androgen formation is regulated by ACTH; thus, excessive secretion can occur either as a "pure" syndrome or as a component of Cushing disease.

The adrenal causes of excess androgen secretion include:

- **Adrenocortical neoplasms** associated with symptoms of androgen excess (virilization) are more likely to be carcinomas than adenomas.
- **Congenital adrenal hyperplasia (CAH).**
 - CAHs represent a group of autosomal recessive disorders, each characterized by a hereditary defect in an enzyme involved in adrenal steroid biosynthesis particularly cortisol.
 - In some forms of CAH; the enzymatic defect impairs aldosterone secretion adding salt loss to virilizing symptoms.

Manifestations of excess androgens:

- a- In boys it leads to precocious puberty with premature development of sex organs.
- b- In girls it leads to enlargement of clitoris, male distribution of hair.
- c- In women it leads to virilism with enlargement of clitoris, amenorrhea and atrophy of breast.

II. Hypofunction of adrenal cortex:

A. Acute adrenal insufficiency:

Causes:

1. Severe haemorrhage which occurs due to severe infections as meningitis (Waterhouse-Friderichsen Syndrome), burns and hemorrhagic diseases.
2. Bilateral surgical removal of adrenals.
3. Individuals with chronic adrenocortical insufficiency may develop an acute crisis after any stress that exceeds their limited physiologic reserves.
4. Rapid withdrawal of steroids

Clinical:

- Shock with low blood pressure
- High fever, pain in the abdomen with nausea, vomiting and diarrhea.
- The condition is usually fatal.

B. Chronic adrenal insufficiency (Addison's disease):

It results from progressive destruction of more than 90% of adrenal cortex of both sides.

Causes:

1. Autoimmune adrenalitis:

- Accounts for 60% to 70% of cases and is by far the most common cause of primary adrenal insufficiency in developed countries.
- In about half of the patients, it is restricted to the adrenal glands (isolated autoimmune Addison disease)
- May be associated with other autoimmune diseases, as Hashimoto disease, pernicious anemia and type I diabetes mellitus.

2. Infections: as tuberculosis, fungi and in AIDS patients (due to several infectious, cytomegalovirus, mycobacterium and noninfectious Kaposi sarcoma).

3. Metastatic neoplasms: The adrenals are a fairly common site for metastases from carcinomas of the lung and breast.

Clinical features and effects:

- Gastrointestinal disturbances are common and include anorexia, nausea, vomiting, weight loss, and diarrhea.
- Increased pigmentation of the skin. In primary adrenal diseases increased levels of ACTH precursor hormone stimulates melanocytes, resulting in hyperpigmentation of the skin and mucosal surfaces. The face, axillae, nipples, areolae, and perineum are particularly common sites of hyperpigmentation.
On the contrary, hyperpigmentation is not seen in individuals with secondary adrenocortical insufficiency.
- Asthenia, muscle weakness and atrophic changes.
- Weak heart beats with hypotension.
- Hyperglycemias, low sodium and high potassium blood level.
- Loss of body hair and growth retardation in children.

III. Adrenocortical neoplasms:

They may be associated with steroid production or non-functioning.

1- Adrenal adenomas:

Most cortical adenomas do not cause hyper-function and are usually encountered as incidental findings.

Gross:

- Adenomas are small, 1 to 2 cm in diameter.
- The cut surface is yellow to yellow-brown (Fig.11.11a).

Microscopic:

- They are composed of cells similar to those of normal adrenal cortex.
- The nuclei tend to be small, although some degree of pleomorphism may be encountered (endocrine atypia).
- The cytoplasm of the neoplastic cells ranges from eosinophilic to vacuolated, depending on their lipid content; mitotic activity is generally inconspicuous (Fig.11.11b).

2- Adrenal cortical carcinomas:

Adrenocortical carcinomas are rare neoplasms that may occur at any age.

Gross: They are large, invasive lesions with variegated cut surface containing areas of necrosis, hemorrhage, and cystic change (Fig.11.12a).

Microscopic:

- Adrenocortical carcinomas may be well-differentiated resembling cortical adenomas or undifferentiated with bizarre cells, and high mitotic activity difficult to distinguish from those metastatic to the adrenal (Fig.11.12b).

Spread:

- Adrenal cancers have a strong tendency to invade the adrenal vein and vena cava.
- Metastases to regional and peri-aortic nodes are common,
- Distant hematogenous spread to the lungs and other viscera. Bone metastases are unusual.
- The median patient survival is about 2 years

NB: Functional and nonfunctional adrenocortical neoplasms cannot be distinguished on the basis of morphologic features.

Metastasis is the only sure evidence of malignancy.

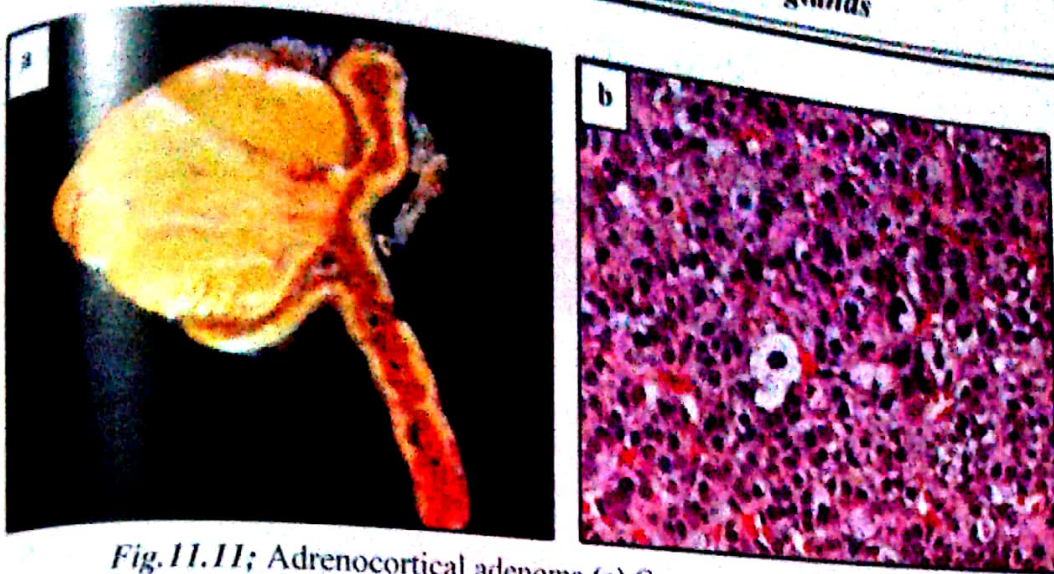


Fig.11.11; Adrenocortical adenoma (a) Gross (b) microscopic

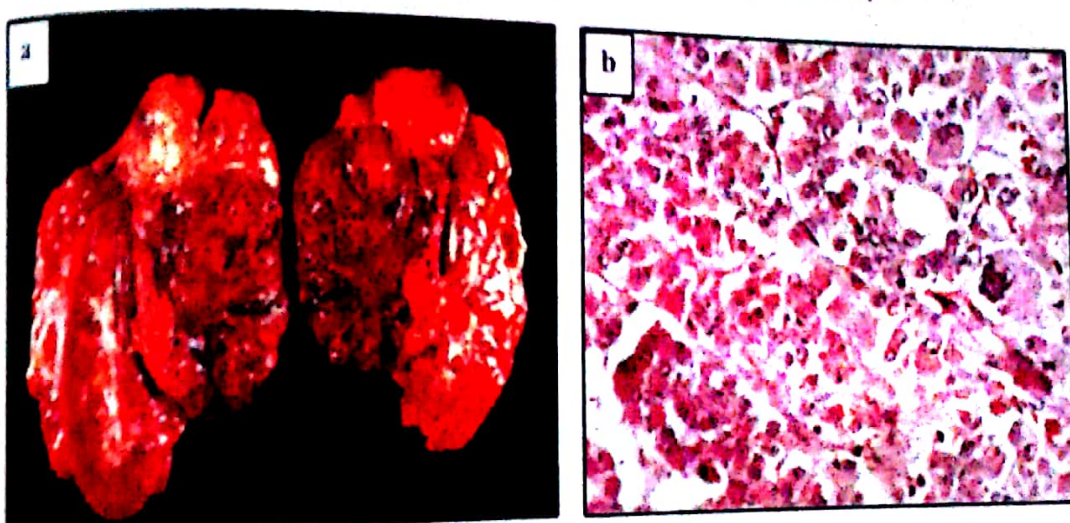


Fig.11.12 : Adrenocortical carcinoma (a) Gross (b) microscopic

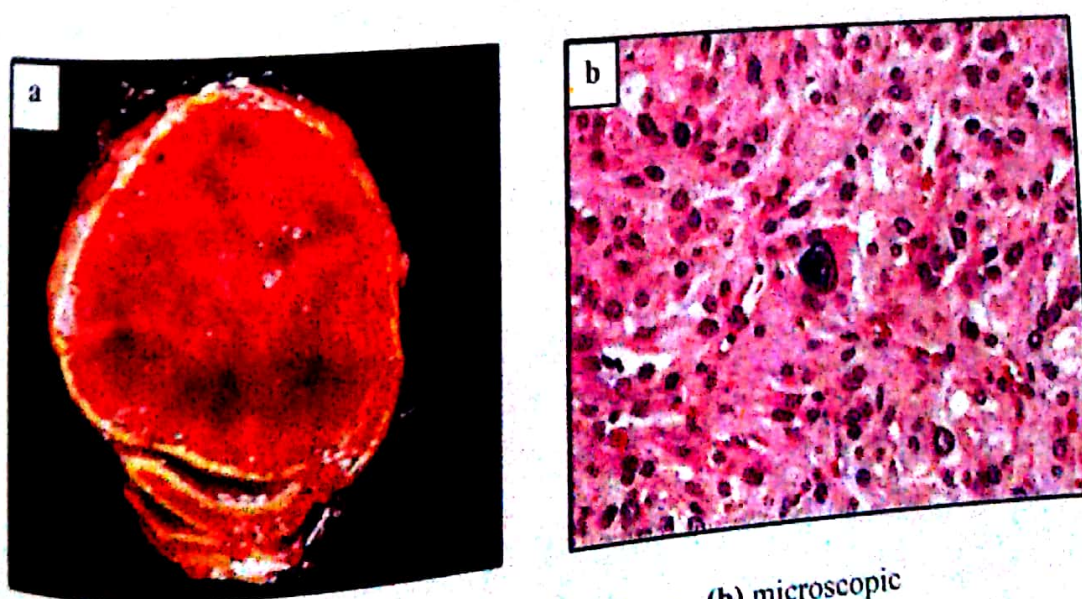


Fig.11.13 : Pheochromocytoma (a) Gross (b) microscopic

B. Adrenal medulla

Most adrenal-medullary disorders are neoplasms, the most significant of which are:

1- Neuroblastoma:

- Neuroblastoma is the most common extra-cranial solid tumor of **childhood**, arising from **neuroblasts**, "embryonic nerve cells".
- These neoplasms occur most commonly during the **first 5 years of life** and may arise during infancy.
- Neuroblastoma may occur anywhere in the sympathetic nervous system and occasionally within the brain, but they are most common in the abdomen; most cases arise in either the adrenal medulla (40%) or the **retroperitoneal** sympathetic ganglia.
- Most neuroblastomas are sporadic, although familial cases also occur.

Gross: The tumor appears as **large, fleshy, greyish-white mass infiltrating the surrounding tissues** with areas of haemorrhage, necrosis and calcification.

Microscopic: The tumor is cellular, formed of **small, dark, round primitive cells arranged in sheets or rosettes (Homer-Wright pseudorosette)**.

Spread:

1. **Local infiltration** to surrounding structures.
2. **Lymphatic spread** to regional lymph nodes.
3. **Hematogenous spread** to skull, orbit and liver.

Neuroblastoms may **secrete catecholamines** other than adrenaline and nor-adrenaline, especially dopamine which appears in urine as **vanillylmandelic acid (VMA)** and **homovanillic acid (HVA)**.

Ganglioneuroma:

It is a rare benign tumor occurring both in children and adults which arises from the ganglion cells.

Pheochromocytoma:

These neoplasms are relatively uncommon, associated with catecholamine production and **hypertension** (surgically correctable form)

Pheochromocytomas usually follow a convenient "rule of 10s":

- **10%** of pheochromocytomas **are extra-adrenal**, occurring in organ of Zuckerkandl and the carotid body, where they are called paragangliomas.
- **10%** of adrenal pheochromocytomas **are bilateral**.

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- 10% of adrenal pheochromocytomas are biologically malignant.
- 10% of pheochromocytomas occur as a part of multiple endocrine neoplasia syndromes (MEN).

Gross: It ranges from small, yellow-tan circumscribed lesions to large, hemorrhagic necrotic, and cystic masses weighing several kilograms.

Microscopic:

- They are composed of polygonal to spindle-shaped chromaffin cells and their supporting cells, divided into small nests, or "Zellballen," by a rich vascular network.
- The cytoplasm of the neoplastic cells often has a finely granular appearance. The nuclei of the neoplastic cells are often pleomorphic.

The definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases (to liver, lung and bone).

Clinical manifestation:

- ❑ Hypertension, with associated increased risk of myocardial ischemia, heart failure, renal injury and cerebrovascular accidents.
- ❑ Clinical features related to the secretion of other hormones as ACTH and somatostatin by the tumor.
- ❑ Diagnosis is by measuring 24 hour urinary catecholamines, vanillylmandelic acid and metanephrines.

Diseases of the thymus

Thymomas:

These are neoplasms arising from thymic epithelial cells, mostly in adults above 40 years, in anterior or superior mediastinum. It may be:

- 1- Benign thymoma; is composed of a mixture of mature epithelial cells and small lymphocytes
- 2- Malignant thymoma.

Type I: It is cytologically benign but invasive (biologically aggressive).

Type II: Squamous cell carcinoma or lymphoepithelioma-like carcinoma.

Diseases of the pituitary gland

I. Tumours

1-Adenomas

Pituitary adenomas are the most common pituitary tumours.

They are classified clinically into;

- 1- Functioning adenomas *characterized by monomorphic infiltration and lack of Reticulin.*
 - ☐ Growth hormone secreting
 - ☐ Prolactin secreting
 - ☐ ACTH secreting
- 2- Non-functioning adenomas *so Reticulin stain is used to differentiate between adenoma and normal tissue.*

General:

- Pituitary adenoma is a well encapsulated soft lesion.
- It may be a microadenoma (less than 1 cm.) or a macroadenoma (larger than 1 cm.).
- It is either localized or invasive adenoma (eroding the sella).

Microscopic:

- Composed of uniform polygonal cells arranged in sheets, papillary, and trabecular patterns with scant vascular stroma. The cytoplasm may be acidophilic, basophilic, or chromophobic.

Clinical:

- Mass effect with visual disturbances.
- Hypopituitarism; nonfunctioning adenoma usually present late as large tumour encroaching on and destroying the anterior pituitary.
- Symptoms and signs related to hormone production.

2- Pituitary carcinoma is very rare

II. Hyperpituitarism

Either due to adenoma or hyperplasia.

Manifestations are:

1. Gigantism due to overproduction of growth hormone before epiphyseal closure characterized by excessive growth in a regular and proportioned manner.
2. Acromegaly It occurs after epiphyseal closure, characterized by overgrowth of bones and soft tissue, organomegaly, diabetes mellitus (in 30% of cases) and hyperthyroidism.
3. Cushing's disease Due to overproduction of ACTH by the pituitary.

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III. Hypopituitarism

It may be primary or secondary to tumours, necrosis or inflammation.

Clinical picture varies according to the age of patient:

1. **Pituitary infantilism**: Occurs in childhood, characterized by **arrested growth and genital hypoplasia**.
2. **Sheehan's syndrome (Post-partum necrosis)**: Circulatory collapse caused by **post-partum haemorrhage** leading to ischaemic necrosis of **anterior lobe**. There is **atrophy of sexual organs and pituitary myxoedema**.

N. B.: **Diabetes insipidus** is due to destruction of posterior lobe of pituitary with **diminished antidiuretic hormone (ADH)**. It may be primary or secondary to head injury, tumours or inflammation (meningitis, T.B. and sarcoidosis). There is marked **polyurea with low specific gravity**.

Multiple Endocrine Neoplasia (MEN):

The MEN syndromes are a group of **autosomal dominant** inherited diseases resulting in proliferative lesions (**hyperplasia, adenomas and carcinomas**) of multiple endocrine organs.

MEN have the following distinctive features:

- They occur at a **younger age** than sporadic cancers.
- They arise in **multiple endocrine organs**, either **synchronously** or **metachronously**.
- Even in one organ, the tumors are often **multifocal**.
- These tumors are usually **more aggressive** and recur in a higher proportion of cases than similar sporadic endocrine tumors.

MEN I: (Werner syndrome); tumours of pituitary gland, thyroid and pancreas.

MEN II (IIa): (Sipple syndrome); medullary carcinoma of thyroid, pheochromocytoma and parathyroid hyperplasia or adenoma.

There is mutation of RET oncogene.

MEN III (Iib): Medullary carcinoma of thyroid, pheochromocytoma and mucocutaneous neuroma.

There is mutation of RET oncogene.

MEN I 3P
→ Parathyroid
→ Pheochromocytoma
→ Pituitary tumors

MEN II 2P+M
→ Para thyroid tumors
→ Pheochromocytoma
→ Medullary carcinoma of thyroid

MEN III 2M+P
→ Medullary carcinoma of thyroid
→ Pheochromocytoma
→ Mucocutaneous neuroma

SUMMARY

Diseases of thyroid gland:

Thyroiditis: Hashimoto's subacute granulomatous and lymphocytic

Goiter: Non inflammatory, non-neoplastic enlargement of thyroid gland

Simple goiter: Endemic goiter, sporadic goiter.

Graves' disease: Thyrotoxicosis, infiltrative ophthalmopathy & dermopathy.

Hypothyroidism: Cretinism, myxoedema

Tumours of the thyroid:

Adenomas: Follicular adenoma and Hurthle cell adenoma

Carcinoma:

1. **Papillary carcinoma** (85%): Papillary and follicular variants.

The nuclear features are diagnostic; they are optically clear nuclei, nuclear grooves and intranuclear cytoplasmic inclusions.

2. **Follicular**

3. **Anaplastic**

4. **Medullary thyroid carcinoma** (C-cell tumour).

Diseases of parathyroid glands:

Primary hyperparathyroidism: Due to adenoma (85%) or to parathyroid hyperplasia (10%, the 4 glands are enlarged).

Skeletal lesions: osteoporosis, osteitis fibrosa cystica & brown tumor.

Secondary hyperparathyroidism: Causes: Chronic renal insufficiency, rickets, osteomalacia, multiple myeloma and metastatic tumours of bone.

Diseases of adrenal glands:

Cushing's syndrome: Due to excess glucocorticoids.

Hypofunction of adrenal cortex:

1- **Acute adrenal insufficiency**: Causes: Severe haemorrhage or surgery

2- **Chronic adrenal insufficiency** (Addison's disease):

Causes: 1. Autoimmune adrenalitis. 2. Infections (TB, fungi, AIDS).
3. Metastatic neoplasms.

Tumours Adrenocortical neoplasms: Adenomas and carcinomas.

Adrenal medullaneoplasms: Neuroblastoma, pheochromocytoma.

Thymomas:

1- Benign thymoma; a mixture of epithelial cells and small lymphocytes

2- Malignant thymoma; Type I: is cytologically benign but invasive.

Type II: squamous cell carcinoma or lymphoepithelioma.

Pituitary adenomas:

• **Functioning adenomas** secrete: growth hormone, prolactin or ACTH

• **Non-functioning adenomas** cause mass effects.

Multiple Endocrine Neoplasia (MEN): A group of autosomal dominant inherited diseases resulting in hyperplasia, adenomas, and carcinomas of multiple endocrine organs.

Chapter 12

Intended Learning Outcomes (ILOs)

By the end of this chapter students should be able to:

- ☐ Classify congenital diseases of bone and list possible complications.
- ☐ Define osteoporosis, explain its pathogenesis.
- ☐ Define osteomyelitis, list its predisposing factors and describe gross and microscopic features.
- ☐ Define Paget disease, explain pathogenesis and list possible complications.
- ☐ Define osteitis fibrosa cystica, explain pathogenesis and list possible complications.
- ☐ Classify bone and cartilage forming tumours and describe the pathological features of each.
- ☐ Classify bone marrow tumours and describe the pathological features of each.
- ☐ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.
- ☐ Identify giant cell tumours and tumour-like conditions of bone.
- ☐ Classify arthritis: explain pathogenesis, describe morphology and list possible complications of each type.
- ☐ Compare and contrast between rheumatoid and osteoarthritis
- ☐ Define gout and pseudogout, explain pathogenesis and describe gross and microscopic features.
- ☐ Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and / or laboratory findings.

DISEASES OF BONES

Anatomical parts of long bones and bone cells (Fig. 12.1a&b)

Hereditary bone disorders:

1- Achondroplasia:

- Achondroplasia is the most common form of dwarfism.
- It is autosomal dominant mutations in fibroblast growth factor receptor 3 (FGFR3), which inhibit cartilage synthesis at epiphyseal plates.

Clinical: Long bones are short and thick leading to dwarfism. Large head and trunk as cranial and vertebral bones are unaffected.

2- Osteogenesis imperfecta "brittle bone disease":

It is an autosomal dominant disorders characterized by defective synthesis of type I collagen.

Clinical: Skeletal deformity, recurrent fractures, blue sclerae, hearing loss and small misshapen teeth.

3- Paget disease (osteitis deformans):

It is characterized by repetitive episodes of:

- Osteoclastic activity and bone resorption (*osteolytic stage*), followed by
- Bone formation (*mixed osteoclastic-osteoblastic stage*), and finally by
- Apparent exhaustion of cellular activity (*osteosclerotic stage*).

The net effect of this process is a gain in bone mass. The newly formed bone is disordered and weak, susceptible to deformity and fracture.

Paget disease usually presents in mid- to late adulthood.

Types: It may be solitary (monostotic) or occur at multiple sites (polyostotic).

Sites: Skull, pelvis, tibia, ilium, femur and vertebrae.

Microscopic: Mosaic pattern due to haphazardly arranged cement lines.

Pathogenesis: Caused by a paramyxovirus infection (a slow virus) that induce IL-1 and IL-6 secretion from infected cells which activate osteoclasts.

About 10% of cases have germ line mutations in the gene *SQSTM1*.

Clinical findings:

- Asymptomatic.
- Bone pain, deformity, fracture, warmth of overlying skin.
- High output heart failure.
- Increased incidence of osteosarcoma.

Osteomyelitis

Osteomyelitis is inflammation of bone and bone marrow.

Types:

- I. Acute pyogenic osteomyelitis:
 - a- Acute haematogenous osteomyelitis.
 - b- Acute non-haematogenous osteomyelitis complicating:
 - ☐ Open fractures.
 - ☐ Surgical operations.
 - ☐ Nearby soft tissue infection.
- II. Chronic osteomyelitis:
 - a- Non specific; as a sequel to acute osteomyelitis.
 - b- Specific:
 - T.B. osteomyelitis.
 - Syphilitic osteomyelitis, it may be congenital or acquired.

I. Acute haematogenous osteomyelitis:

Predisposing factors:

1. **Age:** Common in children (3-10 years).
2. **Sex:** More in boys.
3. **Trauma:** Forms contusion or haematoma.

Causative organisms:

Staphylococcus aureus (the commonest is due to the expression of surface proteins on the surface of Staph that allow its adhesion to bone matrix), also streptococcus, haemophilus influenzae or E. coli.

Route of infection:

Via the blood stream, it follows bacteraemia from septic focus as; tonsillitis, upper respiratory tract infection, abscesses, boils or furuncles

Bones affected:

- The commonest are the tibia, femur and humerus, but any bone could be affected.
- Metaphysis of long bones is more affected because it is more exposed to trauma and blood circulation is slow

Pathological features (Fig. 12.a&b):

1. Acute inflammation, followed by suppuration and necrosis with intermetaphyseal abscess formation.

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2. If not treated, the abscess extends to the surface (subperiosteal abscess), or into the medullary cavity leading to dissemination of the infection throughout the bone with extensive necrosis.
3. The periosteum in children (unlike that of the adult) is loosely attached and the abscess may surround much of the diaphysis leading to tears and thrombosis of penetrating periosteal arteries.
4. Occlusion of both periosteal and endosteal vessels leads to necrosis of some or all of the diaphysis, the dead bone being known as a **sequestrum**.
5. Small sequestra particularly in children tend to be completely absorbed by osteoclastic activity while larger ones usually persist for months or years forming a **nidus** for repeated episodes of infection.
6. As infection becomes less acute subperiosteal new bone known as **involucrum** may form a shell around the dead bone.
7. The involucrum is irregular and often perforated through cloaca allowing pus to track into the surrounding soft tissue ultimately reaching the skin surface and forming a **discharging sinus**.

Complications of acute osteomyelitis:

- a- **Chronic osteomyelitis** due to delay in diagnosis, extensive bone necrosis or inappropriate antibiotic therapy.
- b- **Septicaemia** which leads to **acute bacterial endocarditis**.
- c- **Pyaemia** and acute toxaemia.
- d- **Pathologic fracture**.
- e- **Septic arthritis** in infants and uncommonly in adults.

NB:

- ⊕ The nearby joint is usually spared because the **epiphysis** forms a barrier to **direct spread** from the **metaphysis** and the **periosteum** is firmly attached to the margins of epiphyseal plate.
- ⊕ Spread of infection to nearby joint (septic arthritis) may occur in the following conditions:
 - a- Intra-articular metaphysis e.g. **hip joint**.
 - b- Along tendon passing into a joint e.g. **shoulder joint**.

Complications of chronic osteomyelitis:

- a- **Secondary amyloidosis**.
- b- **Squamous cell carcinoma** of the sinus tract (rare).

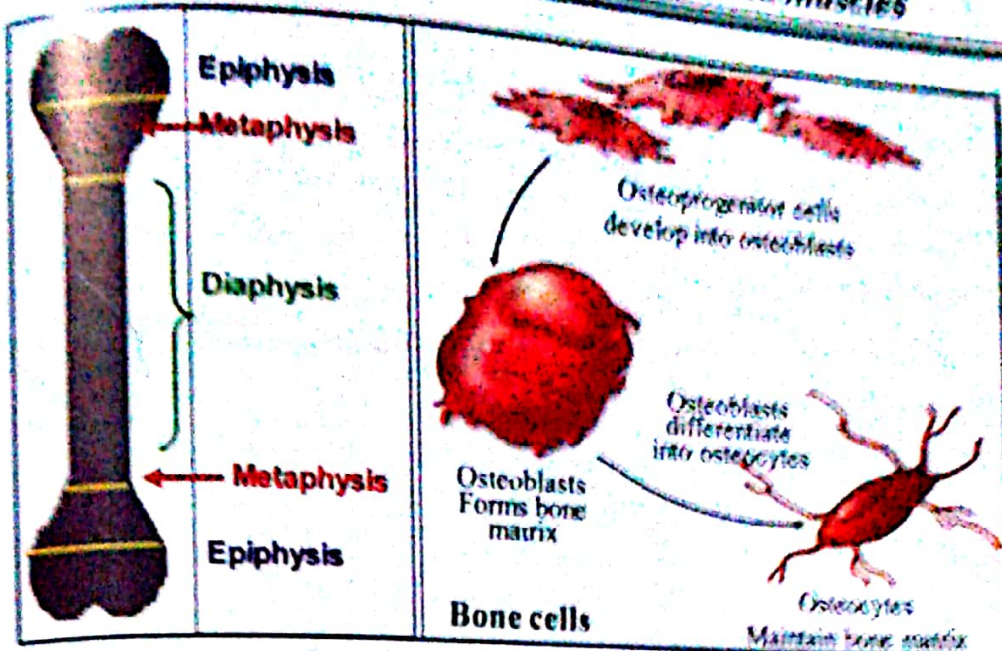


Fig.12.1: (a) Parts of a long bone (b) Bone cells

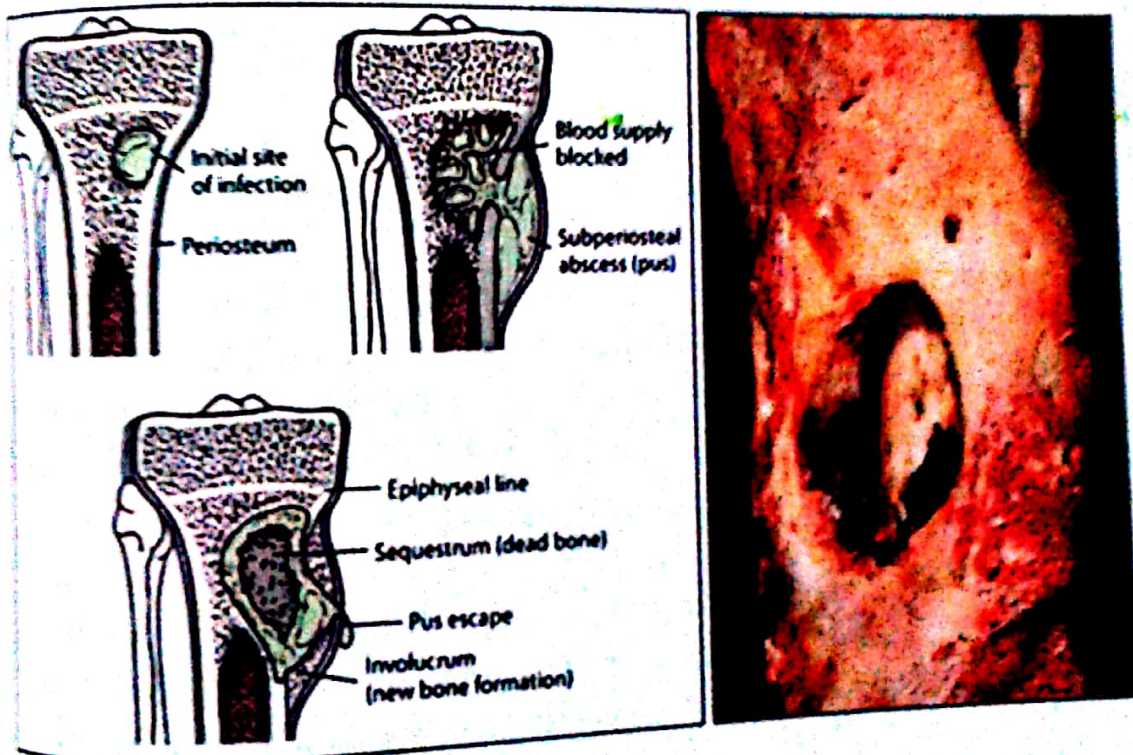


Fig.12.2: (a) Pathology of acute osteomyelitis (b) Osteomyelitis of femur; The drainage tract in the subperiosteal shell of viable new bone (involucrum) reveals the inner necrotic sequestrum (arrow).

Brodie's abscess:

- It is a morphologic variant of osteomyelitis with the following features:
- ❑ It is a localized small intra-osseous abscess that frequently involves the cortex and is walled off by reactive bone.
 - ❑ It is located within the metaphysis mainly at the upper end of tibia and lower end of femur.

II- Tuberculosis of bones:

- ☐ It is a secondary TB (Commonly complicates pulmonary TB).
- ☐ The organisms usually reach the bone through the blood stream.
- ☐ Common in children.
- ☐ It commonly affects the vertebral column, bones of hip, knee, ankle and wrist.

Pott's disease:

It is TB of vertebral column.

Sites: Lower dorsal and upper lumbar or may affect cervical vertebrae.

Morphology: TB reaction with caseation, destruction of vertebral bodies and intervertebral discs (Fig.12.3) and rarefaction of bone (faint X ray shadow).

Complications:

- ☐ Vertebral deformity: kyphosis, scoliosis, lordosis.
- ☐ Collapse with secondary neurologic deficits.
- ☐ Cold abscess:
 - In cervical region; it appears in retropharyngeal space or post triangle of neck.
 - In thoracic region; it appears in intercostal spaces along the ribs.
 - In lumbar region it leads to psoas abscess and may reach inguinal ligament.
- ☐ Paraplegia due to pressure of TB granulation tissue, caseous material or bony specules. When pressure is removed the condition may improve.
- ☐ General complications as:
 - Amyloidosis.
 - Miliary TB.

Diseases associated with abnormal mineral homeostasis:

1- Rickets:

- ☐ It is a disease characterized by deficient mineralization of bone in children (before epiphyseal closure)
- ☐ Caused by vitamin D deficiency which leads to reduced intestinal absorption of calcium.

Vitamin D deficiency may due to:

- a- Malnutrition associated with minimal exposure to sunlight.
- b- Secondary to intestinal malabsorption.

Pathological features:

1. At the growing ends of bone (epiphysis) the normal regular linear arrangement of cartilage cells is replaced in thickets by masses of abnormal proliferating disorganized cartilage.
2. There is abnormal calcification of bony trabeculae with increased amount of uncalcified osteoid, leading to weak soft bone.

Bony manifestations of rickets (Fig. 12.4).

A. Long bones:

1. Widening of the epiphysis of bones e.g. bones of wrist.
2. Bowing of tibia and contracted pelvis.

B. Bones of chest:

1. Masses of osteoid develop at costochondral junctions producing a row of small lumps on either side of the sternum (rachitic rosary).
2. A transverse groove (Harrison's sulcus) is seen on the ribs denoting the site of insertion of diaphragm with pulling of soft areas of ribs.
3. Pigeon chest deformity due to inward pull of the ribs by the intercostal muscles and forward protrusion of the sternum.

C. Vertebral column: Deformity of spine (lumbar lordosis).

D. Skull:

1. Bossing in frontal and parietal bones.
2. Delayed closure of sutures and fontanelles.
3. Delayed eruption of teeth.

II- Osteomalacia:

- ❑ It is defective mineralization of bone in adults (after growth is completed).
- ❑ Due to either dietary deficiency or abnormal metabolism of vitamin D which prevents Ca absorption from the bowel.
- ❑ Osteomalacia causes bone pain but gross skeletal deformities are rare.

III. Hyperparathyroidism (Osteitis fibrosa cystica):

Causes:

- Hyperparathyroidism is either primary (due to parathyroid hyperplasia or adenoma) or secondary (due to prolonged status of hypocalcaemia resulting in compensatory hypersecretion of parathyroid hormone).
- The increased parathyroid hormone levels are detected by receptors on osteoblasts which initiate the release of mediators that stimulate osteoclastic activity.

Pathological features:

- The cortical bone is greatly thinned.
- Microfractures and secondary haemorrhages occur and elicit an influx of multinucleated macrophages and reactive fibrous tissue to form the *brown tumour*. This brown colour is due to vascularity, haemorrhage and haemosiderin deposition (Fig.12.5).
- These lesions undergo cystic degeneration.



Fig.12.3: Pott's disease, destruction of vertebral bodies & discs

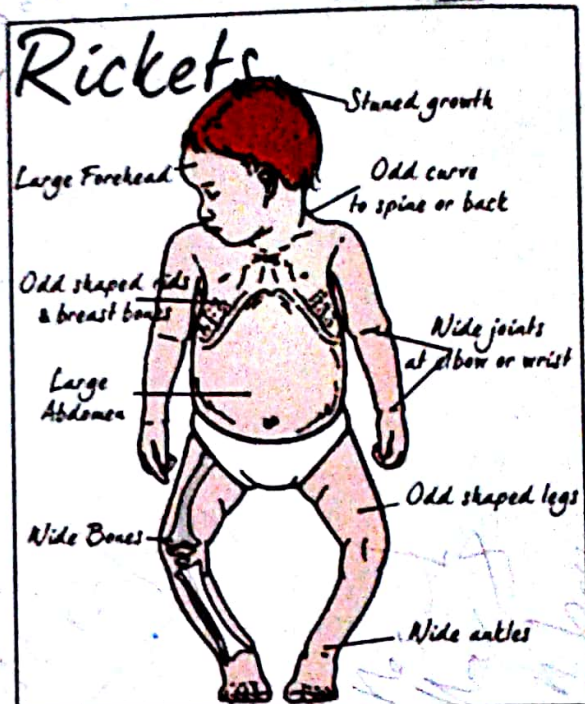
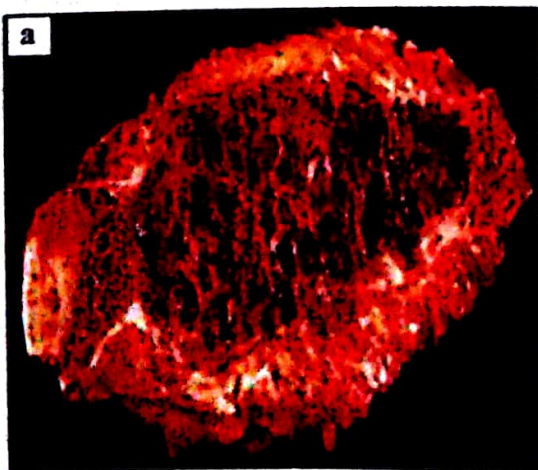
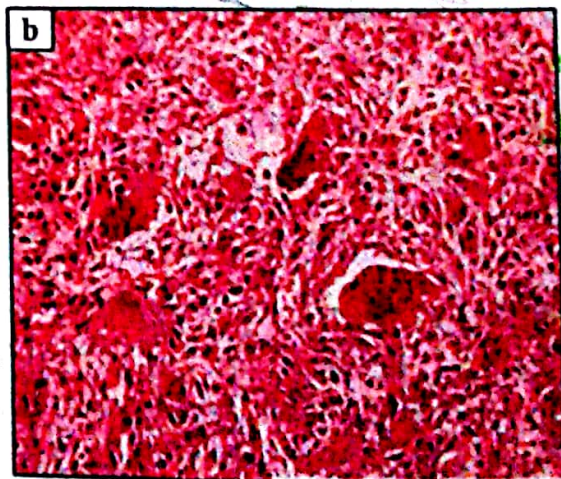


Fig.12.4: Bony manifestations of rickets



(a) Resected rib harbouring an expansile brown tumour



(b) Brown tumor; giant cells & fibrosis.

Fig.15.5: Hyperparathyroidism

Bone tumours

Benign

I. Primary tumours:

A. Bone forming tumors:

1. Osteoma
2. Osteoid osteoma.
3. Osteoblastoma

Malignant

Osteosarcoma.

B. Cartilage forming tumors:

1. Chondroma.
2. Osteochondroma.
3. Benign chondroblastoma.
4. Chondromyxoid fibroma.

Chondrosarcoma

C. Fibrous tumours: Fibrosarcoma

D. Vascular tumours:

Haemangioma.

Haemangiosarcoma.

E. Myelogenic tumours: Both are malignant

1. Plasma cell myeloma.
2. Ewing's tumour.

F. Bone lymphoma: Hodgkin's and non-Hodgkin's type.

G. Unknown: Giant cell tumour.

II. Metastatic tumours:

Bone forming tumours:

1- Osteoma (Compact or ivory osteoma):

It is a slow-growing tumour of membranous bones.

Age: 40 - 50 years.

Sex: Slight male predominance.

Affected bone: Common in the skull, but can occur in any bone.

Gross:

- The lesion may be single or multiple.
- The lesion consists of a very dense compact bone, appears as hard smooth, rounded or lobulated sessile mass (Fig.12.6a).

Microscopic: It consists of a mixture of lamellar and woven bones (Fig.12.6, b).

Effects: It may arise from:

1. Outer table of skull causing disfigurement.
2. Inner table of skull causing pressure manifestation:
 - a- In skull vault it may cause pressure on eye ball (proptosis).
 - b- In the orbit it may cause pressure on eye ball (proptosis).

- c- In paranasal sinus may lead to sinusitis.
- d- In auditory meatus causing conductive deafness.

2- **Osteoid osteoma:**

It is a benign, painful tumour.

Age: 10 - 30 years.

Sex: Affects males more than females.

Affected Bone: Common in the femur and tibia, but occurs in any bone.

Site: In the cortex of metaphysis.

Radiography: A small radiolucent area (nidus), up to 1.5cm in diameter, surrounded by dense sclerotic reactive bone.

Gross: The nidus appears entirely in the cortex. It is oval globular with well-defined edges. The lesion is brownish red and granular (Fig.12.7a).

Microscopic:

- The nidus consists of an interlacing network of osteoid trabeculae arranged in a haphazard manner and rimmed by osteoblasts.
- Between the osteoid trabeculae, there is a loose fibrovascular connective tissue (Fig.12.7 b).

3- **Osteoblastoma:**

Age: 10 - 30 years.

Affected Bone: The vertebrae being the commonest location, but occurs all over the skeleton.

Site: Medulla of metaphysis.

Radiography: Radiolucent area as osteoid osteoma but lacks the surrounding reactive bone. It is larger, exceeding 2 cm in diameter.

Microscopic: Osteoblastoma is indistinguishable from the central nidus of osteoid osteoma (Fig.12.7b, table.12.1).

Table.12.1: Differences between osteoid osteoma and osteoblastoma.

	Osteoid osteoma	Osteoblastoma
Size	Less than 2 cm	More than 2 cm
Site of lesion	Cortex of long bones as femur & tibia	Most often in vertebra. Medullary cavity of long
Pain	Nocturnal pain relieved by aspirin	Dull achy pain not responsive to aspirin
Bone reaction	Surrounded by dense bone reaction	Little or no bone reaction

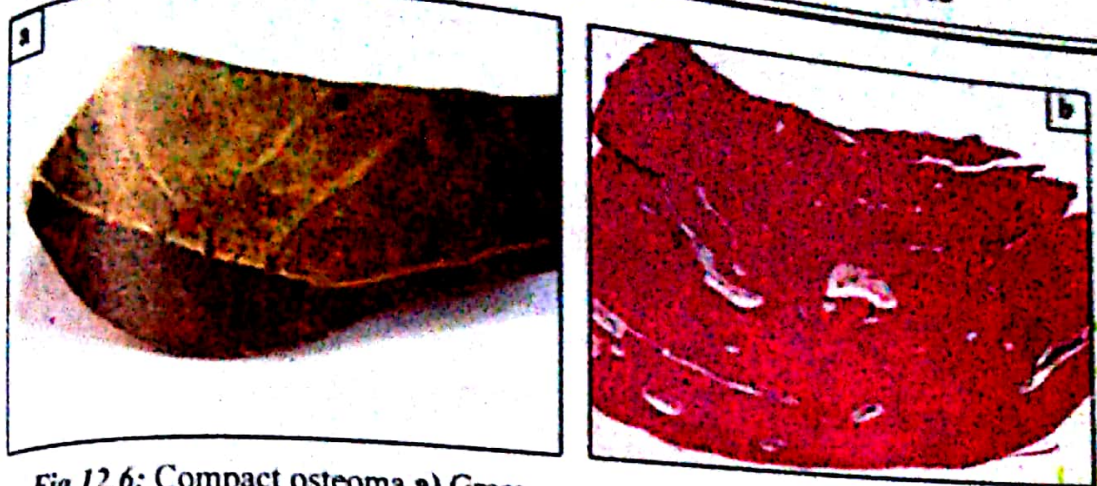


Fig.12.6: Compact osteoma a) Gross

b) Microscopic

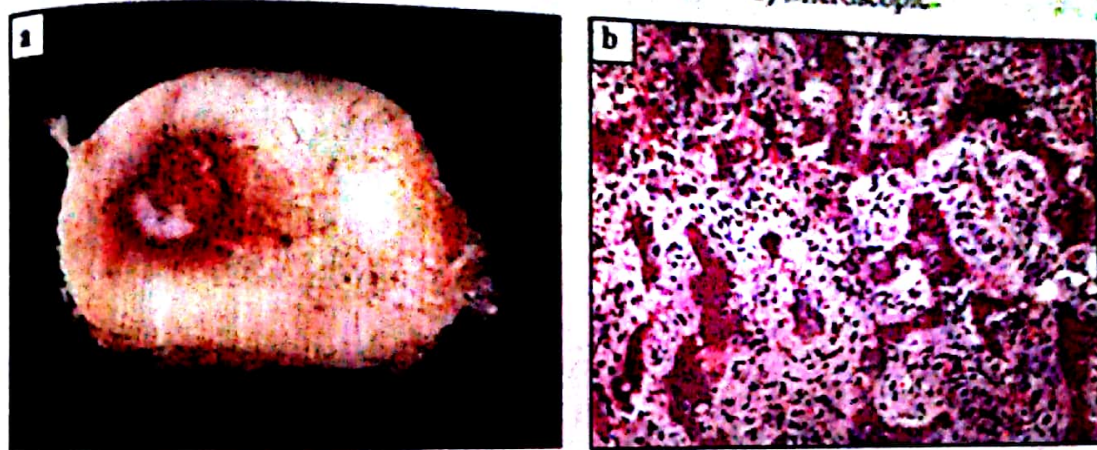


Fig.12.7: Osteoid osteoma a) Gross

b) Microscopic appearance

Osteosarcoma:

- It is the **most common** primary malignant tumour of bone of a high-grade malignancy. It produces **osteoid matrix**.
- Osteosarcoma is divided into:

1-Primary osteosarcoma

Age: Common in the second decade of life (10 - 25 years).

Sex: Males are more affected than females.

Bone affected: Lower part of femur, upper part of tibia, but can affect any bone (Fig.12.8).

Site: Metaphysis (in its medulla)

2-Secondary osteosarcomas: Occur in older age, usually in association with Paget's disease, bone infarcts, previous radiation or benign tumours.

Radiography: The lesion may be:

1. Osteoblastic:

The lesion appears as soft tissue shadow with ill-defined margins due to

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early cortical destruction and infiltration of medulla. It may give:

- a- **Sun-rays" appearance**; in which the neoplastic bone arise perpendicular to the long axis of the bone (*Fig.12.9*).
- b- **Codman's triangle**; in which reactive new bone formation is present at the junction where the periosteum has been lifted off the cortex by the tumour (*Fig.12.10*).
- Epiphyseal plate is usually intact (not invaded).

2. **Osteolytic**: Predominantly radiolucent or have a mixed pattern.

Gross:

- It forms a large mass extending into bone marrow and the soft tissues.
- The lesion is soft and fleshy or gritty depending on the amount of osteoid produced.
- It is tan-white and often contains areas of hemorrhage and cystic degeneration (*Fig.12.11*).
- It may cause pathological fracture

Microscopic:

- The tumour cells (**malignant osteoblasts**) have large hyperchromatic nuclei, bizarre tumour giant cells and atypical mitoses.
- The **osteoid matrix** is in the form of a fine lace-like pink matrix characteristically rimmed by the neoplastic cells (*Fig.12.12*).

Microscopic types of osteosarcoma:

1. **Conventional osteosarcoma**: It is subdivided into: osteoblastic, fibroblastic (about 25%) and chondroblastic depending on the predominant matrix whether osteoid, fibrous or chondroid.
2. **Telangiectatic osteosarcoma** with many vascular spaces.
3. **Low-grade (parosteal) osteosarcoma**.
4. **Small cell osteosarcoma**

Grading (I – III) is based on the degree of anaplasia.

Spread:

1. **Direct spread**:
2. **Blood spread**:

It tends to spread early by blood and it is not uncommon that the patient has lung metastases at time of presentation.

3. **Lymphatic spread**: does not occur.

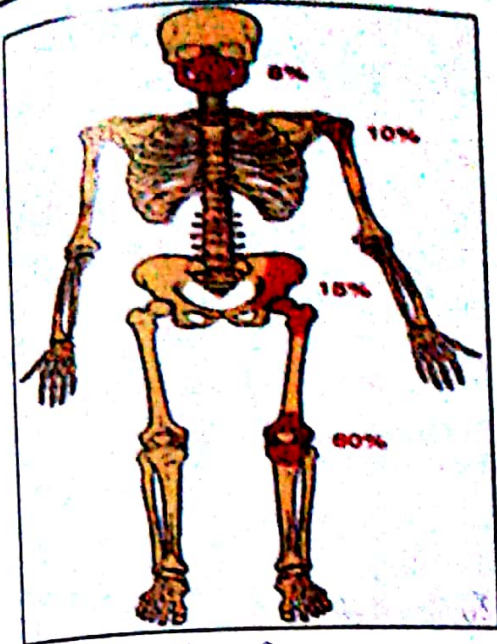


Fig.12.8: Sites of osteosarcomas.



Fig.12.9: Osteosarcoma Sun-ray appearance

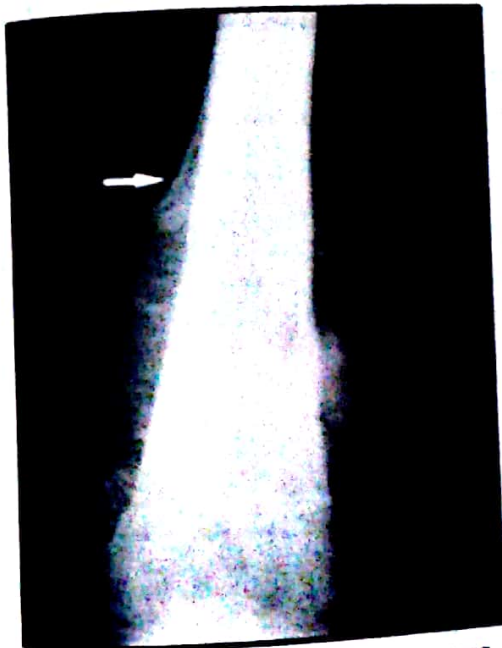


Fig.12.10: Distal femur osteosarcoma Note Codman triangle (arrow)



Fig.12.11: Osteosarcoma, fills the medullary cavity & infiltrates the cortex.

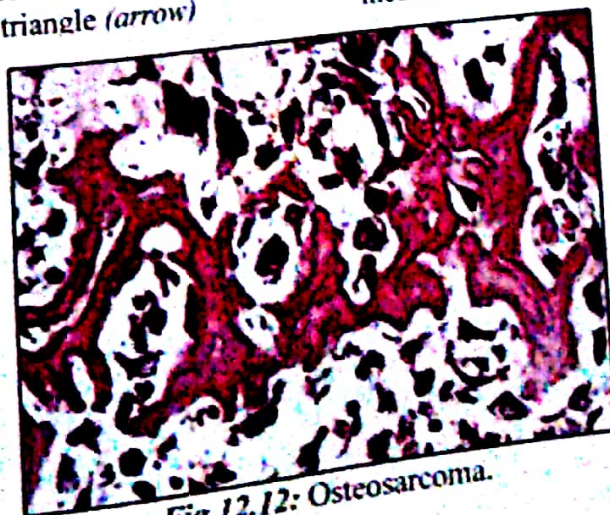


Fig.12.12: Osteosarcoma.

Cartilage forming tumours:

1- Chondroma:

- It is a benign neoplasm which is composed of hyaline cartilage.
- It may arise within the bone (medullary cavity) known as **enchondroma**, or on the surface of bone (**juxtacortical chondroma**) or in the soft tissue (soft tissue chondroma). Enchondroma may be multiple (**Multiple enchondromatosis**) as in Ollier disease.

2- Enchondroma:

Age: Most frequent in the third to fifth decades of life.

Sex: It occurs equally in the both sexes.

Affected Bone: - Mainly tubular bone as short bones of hands and feet.
- Long bones as femur and humerus.

Site: Medulla of diaphysis. (Originate from heterotopic cartilagenous cell nests in the medullary cavities).

Radiography: A central radiolucent lesion with a well defined margin.

Gross: The lesion is well-circumscribed, lobulated and pale blue with honey-comb appearance (*Fig.12.13a*).

Microscopic: It is composed of lobules of hyaline cartilage of low cellularity with rare double nucleated cells (*Fig.12.13b*).

3- Osteochondroma (exostosis):

It is the most common benign bone tumour.

Age: Childhood and adolescent (10 - 30 y).

Sex: Males are affected three times more often than females.

Affected bone: Common in long bones (lower femur and upper tibia).

Site: Metaphysis of long bones. It starts in its cortex near the epiphyseal plate, and then grows away.

The tumour is usually solitary but can be multiple.

Radiography: A mushroom - like growth which grows away from the nearest joint. The cortex of the underlying bone is continuous with the cortex of the stalk of osteochondroma. Similarly, the medullary cavity is continuous with medullary cavity of the stalk (*Fig.12.14*).

Gross: It consists of a cartilage - capped bony protrusion.

Microscopic: The cartilaginous cap which is formed of chondrocytes arranged in a linear fashion. Underneath the cartilaginous cap there is trabecular bone with ossification of the matrix. The intertrabecular space is filled with fatty or haematopoietic marrow.

Chapter 12: Diseases of bones, joints and muscles

Complications:

- Secondary chondrosarcoma.
- Fracture of stalk.

+ Benign chondroblastoma:

Age: Under 20 years.

Sex: More in males.

Sites: Epiphyseal region.

affected bones: Distal femur, proximal tibia and proximal humerus.

Radiography: Well-circumscribed radiolucent lesion that may show calcification.

Gross: A greyish white granular mass.

Microscopic (Fig.12.15):

- Highly cellular and the dominant cells are chondroblasts (Uniform, small round cells with abundant cytoplasm).
- Multinucleated osteoclast giant cells are seen.
- Calcification is common (Chicken-wire calcification).



Fig.12.13: Chondroma of small bones of hand (a) Gross, (b) Microscopic.

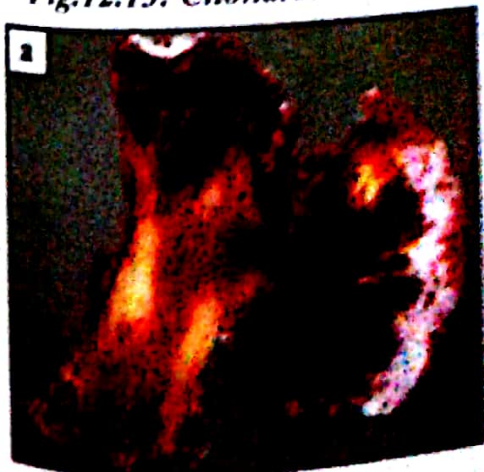


Fig.12.14: Osteochondroma
Mushroom-like growth.

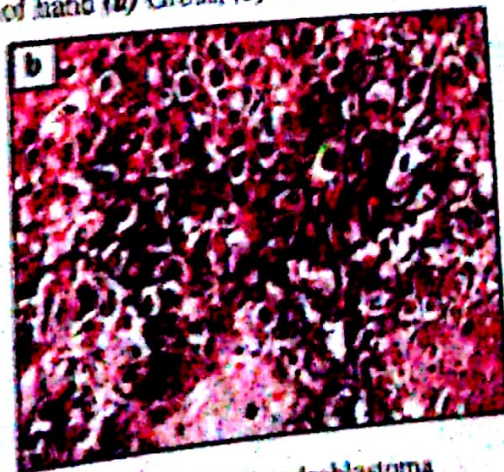


Fig.12.15: Chondroblastoma
note chicken-wire calcification.

Chondrosarcoma:

- It is the third most common type of malignant bone neoplasm (being less common than myeloma and osteosarcoma).
 - It is divided into:
 1. Primary chondrosarcoma (conventional chondrosarcoma).
 2. Secondary chondrosarcoma: It occurs on top of or in association with a pre-existing enchondroma, osteochondroma, chondroblastoma, fibrous dysplasia and Paget's disease.
- It is of a low grade and prognosis is excellent.

Age: 40 - 60 years.

Sex: Males are affected more than females.

Affected Bones: There is predilection to pelvic bones, shoulder girdles and ribs. Also femur and tibia are affected.

Sites:

1. Central cavity of diaphysis or metaphysis.
2. Peripheral cortical or subperiosteal, may occur on top of osteochondroma.

Radiography:

- Radiolucent with speckled calcifications which appear as diffuse "Salt and Pepper" or more discrete "Popcorn" pattern.
- It produces expansion of the bone with thickening of the cortex (low grade tumors) or destruction of cortex (high grade lesions).

Gross: Pearly white mass or light blue appearance of cartilage with foci of calcification, myxoid degeneration with small cyst formation may be seen (Fig.12.16a).

Microscopic:

- Malignant chondrocytes with plump multinucleated lacunae are scattered within a chondroid matrix.
- The nuclei are crowded together with double nucleation, hyperchromasia, and multiple nucleoli.
- The tumour retains a lobulated appearance (Fig.12.16b).
- Chondrosarcoma is graded as 1-3 according to cellularity, cytologic atypia and mitotic figures.
- **Tumour marker:** S100.

Microscopic variants of chondrosarcoma:

1. Conventional chondrosarcoma; is the most common variant and is composed of malignant hyaline cartilage.

- Chapter 12: Diseases of bones, joints and muscles**
2. Clear cell chondrosarcoma.
 3. Dedifferentiated chondrosarcoma.
 4. Mesenchymal chondrosarcoma.
 5. Myxoid chondrosarcoma.

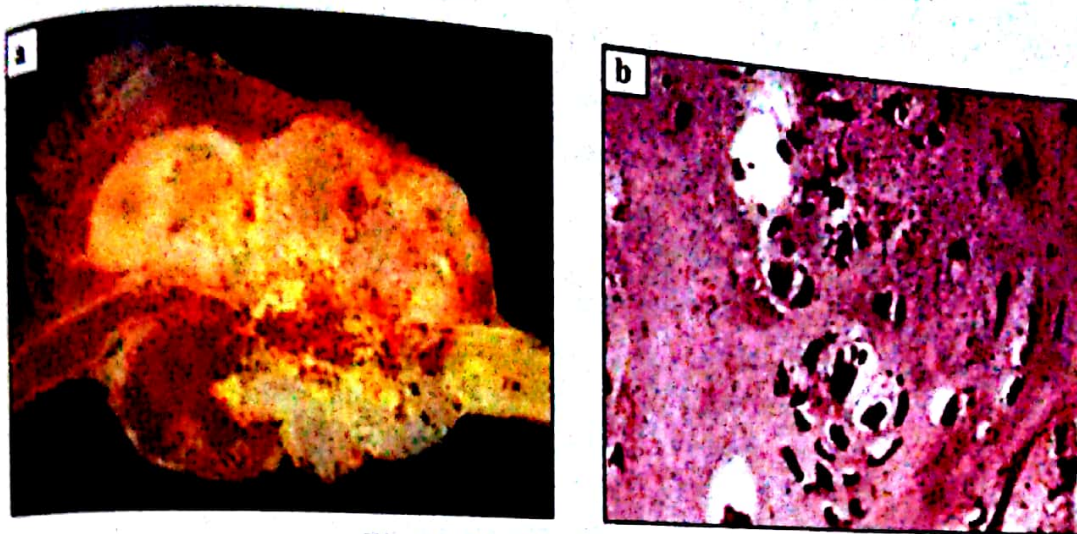


Fig.12.16: Chondrosarcoma

(a) Grossly infiltrating soft tissue (b) Anaplastic chondrocytes in a chondroid matrix

Myelogenous tumours:

Plasma cell myeloma:

- The most common bone neoplasm, accounting for one-third of all bone neoplasms.
- It arises from the plasma cells of the bone marrow.
- Plasma cells secrete an osteoclast stimulating factor that activates bone resorption.

Age: 40 - 60 years.

Sex: Males are more affected than females.

Affected Bones: Any bone containing haematopoietic marrow e.g. spine, ribs, skull and pelvis.

Radiography:

- Multiple punched-out, purely lytic holes in the bone (Fig.12.17a).
- It is not associated with any sclerosis.

Gross: The tumour is soft and red i.e. current jelly appearance.

Microscopic:

- It consists of sheets of immature plasma cells with eccentric nuclei, clumped chromatin and abundant amphophilic cytoplasm (Fig.10.17b).
- Markedly atypical nuclei and abundant binucleated cells are often present.
- Some myelomas contain deposits of amyloid which may be in the wall of vessels or present as masses within the tumour.

Types of myeloma:

1. Solitary myeloma.
2. Multiple myeloma.

Laboratory findings:

- Serum and urine immunoelectrophoresis reveals immunoglobulin spike and Bence Jones proteins in 99% of cases.
- Hypercalcaemia and hyperuricaemia are common.

Clinical features and effects:

1. Pathological fracture of bone.
2. Light chain proteins are deposited in tissues as amyloid material.
3. Renal insufficiency due to deleterious effects of Bence Jones proteins on renal tubular cells, hypercalcaemia, infection and amyloidosis.
4. Anaemia and thrombocytopenia due to bone marrow replacement by the tumour tissue.
5. Hypercalcaemia and metastatic calcification due to bone destruction.

Ewing's Sarcoma (Primitive neuroectodermal tumour-PNET):

It is a highly malignant bone tumour arising from the neuroectodermal cells of bone marrow.

Age: 5 - 20 years.

Sex: Males are more affected than females.

Site: Diaphysis of long bones.

Affected bones: Commonly the tibia, femur and iliac bones.

Radiography: Destructive radiolucent lesion with subperiosteal reactive new bone formation giving rise to "onion skin" appearance (layers of new bone formation parallel to long axis)

Gross: The neoplasm is soft and friable with areas of necrosis and haemorrhage (Fig.12.18a).

Microscopic:

- Made up of diffuse sheets of small round to oval cells with hyperchromatic nuclei and scanty cytoplasm.
- Mitotic figures are numerous.
- The presence of glycogen in cytoplasm of cells gives positive reaction with Periodic Acid Schiff (PAS) stain.
- The cells may arrange themselves around blood vessels in pseudorosette fashion (Fig.12.18b).
- **Tumour markers:** CD99.

N.B.: Ewing's tumour presents with pain and tends to spread early by blood and to surrounding soft tissues.

Bone Lymphoma:

Non-Hodgkin's Lymphoma:

Primary non-Hodgkin's lymphoma is relatively rare, it is usually of large cell type similar to that in nodal sites. But disseminated lymphoma commonly involves the bone.

Age: It is common in adults.

Sex: No sex predilection.

Site: Diaphysis or metaphysis of long bones.

Radiography: Patchy cortical and medullary destruction.

Prognosis: Is relatively good.

Tumour Markers: LCA, CD 20, CD3.

Giant cell tumour of bone:

It is primary bone tumour that contains a large number of multinucleated osteoclast type giant cells admixed with neoplastic mononuclear stromal cells, giving rise to the synonym "Osteoclastoma".

Age: 20 - 40 years.

Sex: Slight female predominance.

Affected Bone: Lower end of femur and radius, upper end of tibia and humerus, but any bone can be affected.

Site: Epiphysis.

Radiography: It appears as a radiolucent mass expanding the bone with thinning of cortex. The mass is traversed by thin sclerotic lines giving soap bubble appearance.

Gross:

- The tumour is soft and dark brown with a fleshy consistency.
- Cyst formation is often seen (Fig.12.19a).
- It expands the bone with thinning of cortex giving egg-shell crackling sensation.

Microscopic:

- It consists of multinucleated osteoclast-type giant cells and neoplastic stromal small oval or spindle-shaped cells.
- The giant cells are distributed uniformly and contain numerous nuclei up to 100 nuclei and abundant eosinophilic cytoplasm.

Microscopic grading:

Grade I: (Benign).

Multinucleated giant cells dominate the picture and stromal cells are bland, (Fig.12.19b).

Grade II: (Locally aggressive).

The stromal cells are spindle - shaped with marked cellular atypia and infrequent mitoses. The giant cells are decreased in number.

Grade III: (Malignant).

The stromal cells are anaplastic with high mitotic activity.

N.B.:

- The microscopic grading of giant cell tumour is not of great value except for the obviously sarcomatous (grade III lesion). This is because metastases can occur in grade I tumours.
- So giant cell tumour of bone should be regarded as: **Potentially low grade malignancy:** Because of their tendency to recur (50%) and their occasional capacity for metastases (10%) regardless of the histological appearance.

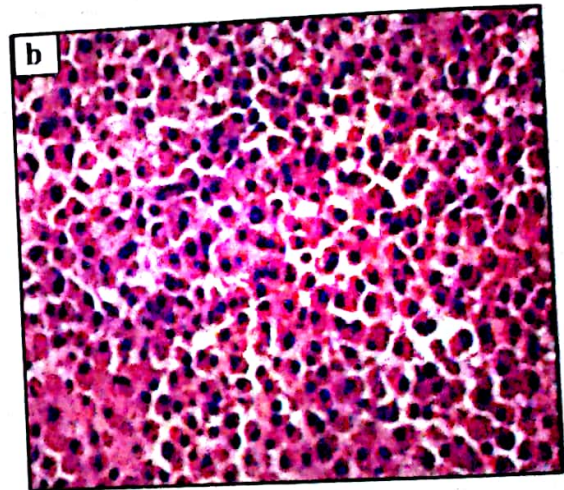
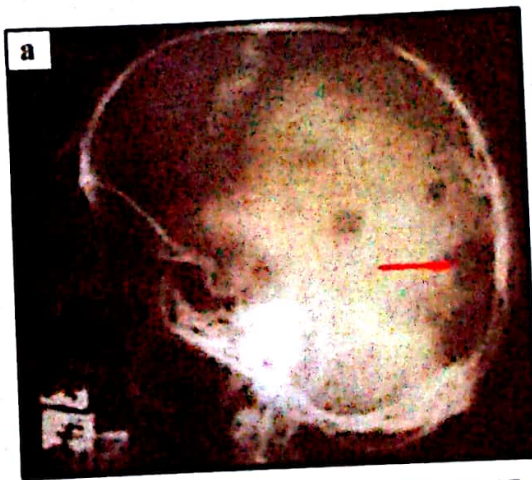


Fig.12.17: Multiple myeloma;

(a) Lytic skull lesions

(b) Sheets of immature plasma cells

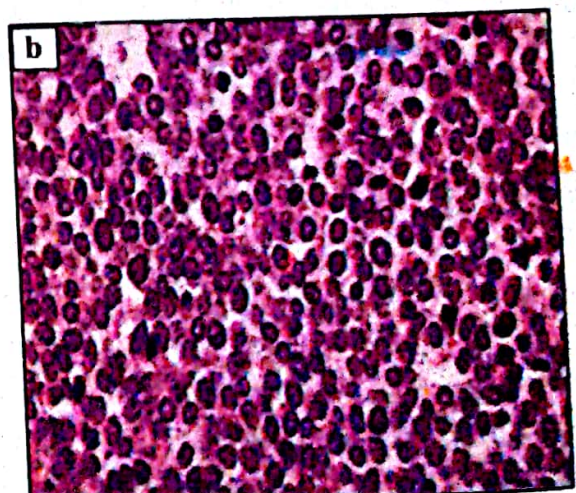
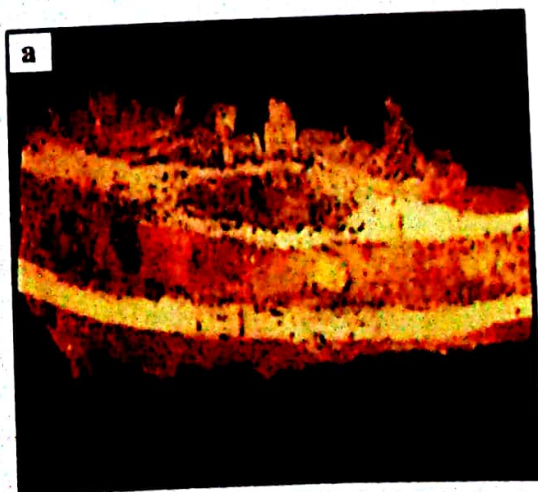


Fig.12.18: Ewing's sarcoma

(a) Diaphyseal soft friable tumour

(b) Diffuse sheets of small round cells



Fig.12.19: *Giant cell tumour of bone*
 (a) Soft and dark brown tumour
 (b) Numerous giant cells & bland stromal cells

Diseases of the joints

Arthritis:

It is inflammation of the joints. It may be acute or chronic.

I. Acute Arthritis:

A. Acute non suppurative arthritis:

1. Rheumatic arthritis.
2. Traumatic arthritis.
3. Toxic arthritis in diphtheria.

B. Acute suppurative arthritis.

II. Chronic arthritis:

A. Chronic non specific arthritis.

B. Chronic specific arthritis: e.g. tuberculosis, syphilis, and rheumatoid arthritis.

Acute arthritis:

Acute suppurative arthritis:

Age: All ages, but more common in children.

Sex: Males are affected more than females.

Causative organism: Staphylococcus, Streptococcus, gonococci, H. influenza or salmonella.

Predisposing factors:

- A. General: Generalized lower resistance.
- B. Local: Trauma causing contusion or hematoma.

Routes of infection:

1. Via blood stream.
2. Penetrating wounds and intra-articular injection.
3. From a nearby infection as in osteomyelitis.

Affected joints: Any joint, but the knee and hip joints are the most common.

Chronic arthritis:

1. Tuberculous arthritis

Commonly affect hip and knee joints.

Routes of infection

- Direct extension from TB of nearby bone.
- Hematogenous infection.

Pathological lesions

- TB reaction with thickening of synovial membrane and destruction of articular cartilage, the underlying bone is exposed and rarefied.
- Effusion of joint.
- Cold abscess and sinus formation.

Complications

- Fibrosis resulting in stiff joint.
- Hematogenous spread leading to miliary TB.
- Amyloidosis.

2. Rheumatoid arthritis (RA)

It is a chronic systemic inflammatory disorder that may affect many tissues, but principally attacking the joints causing non suppurative proliferative synovitis producing permanent injury and deformity.

Pathogenesis:

- The joint inflammation is immunologically mediated (autoimmunity).
- There is clear genetic predisposition to the disease.
- The initiating agent is not yet understood.

Age: The peak incidence is in the 3rd - 4th decades, but no age is immune.

Sex: Women three to five times more often than men.

I- Joints: Symmetric arthritis principally affecting small joints of hands and feet. Lesions of larger joints appear later.

Gross: The synovium becomes oedematous, thickened and is thrown into villous folds matted by fibrin.

Microscopic (Fig.12.20):

- Chronic synovitis characterized by **pannus** formation.

The pannus is formed of;

- Proliferated synovial cells with villous projections.
- Inflammatory cells rich in plasma cells and lymphoid follicles.
- Granulation tissue and fibrosis.

The pannus fills the joint cavity, destroying articular cartilage, eroding the underlying bone with subsequent fibrosis, calcification and permanent ankylosis.

Destruction of tendons and ligaments and joint capsule produce the characteristic deformity

II. Systemic manifestations:

1. **Skin:** Rheumatoid subcutaneous nodules arise in regions which are subjected to pressure such as ulnar aspect of forearm, elbows, occiput and lumbosacral area. These nodules are firm, and not tender.

2. **Blood Vessels:** Vasculitis particularly end arteritis and may lead to skin ulcers, Raynaud's phenomenon and peripheral neuropathy.

3. **Lung lesions:** e.g. pleuritis with pleural effusion, large rheumatoid nodules in lung and diffuse or nodular pulmonary fibrosis.

4. **Ocular lesions** e.g. keratitis, scleritis or granulomatous uveitis.

5. **Myocardium** is rarely involved (arrhythmias) and pericarditis occurs in 10%.

6. **Amyloidosis:** It is one of commonest causes secondary amyloidosis.

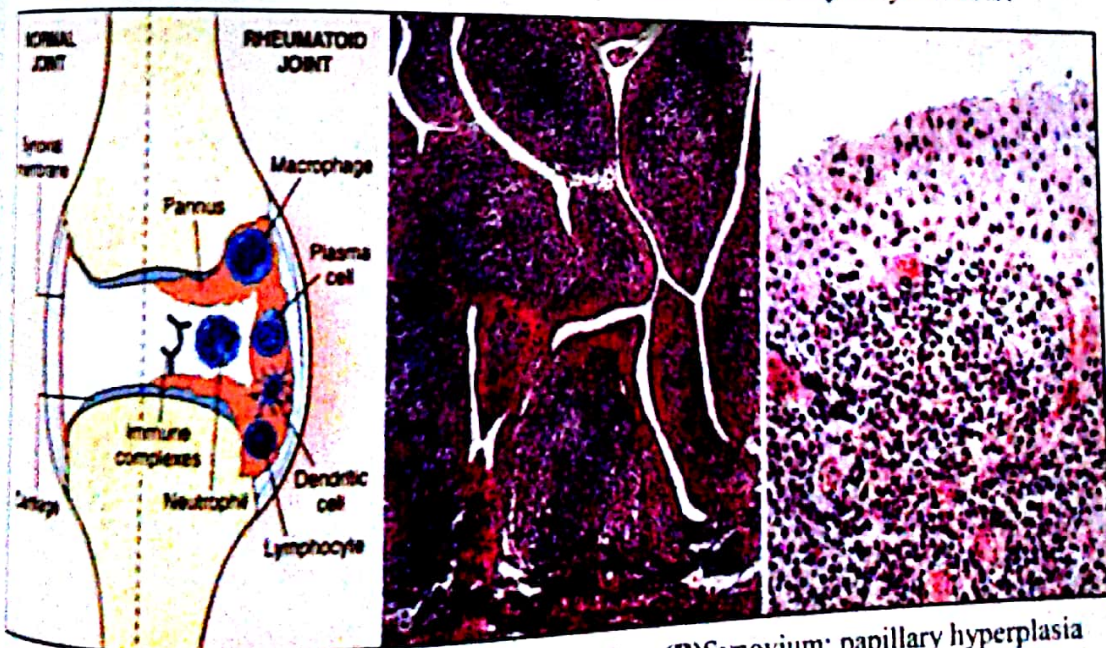


Fig.12.20: Rheumatoid arthritis (A) Joint lesion. (B) Synovium; papillary hyperplasia (C) Hypertrophied synovitis with underlying lymphocytes & plasma cells

Osteoarthritis:

It is a degenerative non-inflammatory joint disease: characterized by progressive erosion of articular cartilage.

Pathogenesis (Fig.12.21):

Primary osteoarthritis: Most common, an aging phenomenon.

Secondary osteoarthritis: In minority of cases, it may appear in younger

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individuals with predisposing conditions such as traumatic injuries to a joint, obesity, diabetes and genetic factors.

- Both of the above conditions affect chondrocyte function which is critical to maintain cartilage synthesis and degradation.
- **Affected joints:** Large joints as hip joint, knee and vertebral joints.

Gross (Fig.12.22):

- ❑ The articular surface appears soft and granular.
- ❑ Full thickness portions of the cartilage are sloughed and the subchondral bone plate is exposed.
- ❑ Friction smooths the exposed bone, giving it the appearance of polished ivory (bone eburnation).
- ❑ Mushroom-shaped cartilagenous excrescences arise at the margins of the articular surface. They gradually ossify forming osteophytes

Microscopic:

- The chondrocytes proliferate forming "clones".
- The synovium is congested and fibrotic and may have scattered chronic inflammatory cells.

NB: Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis shown in (Fig.12.23).

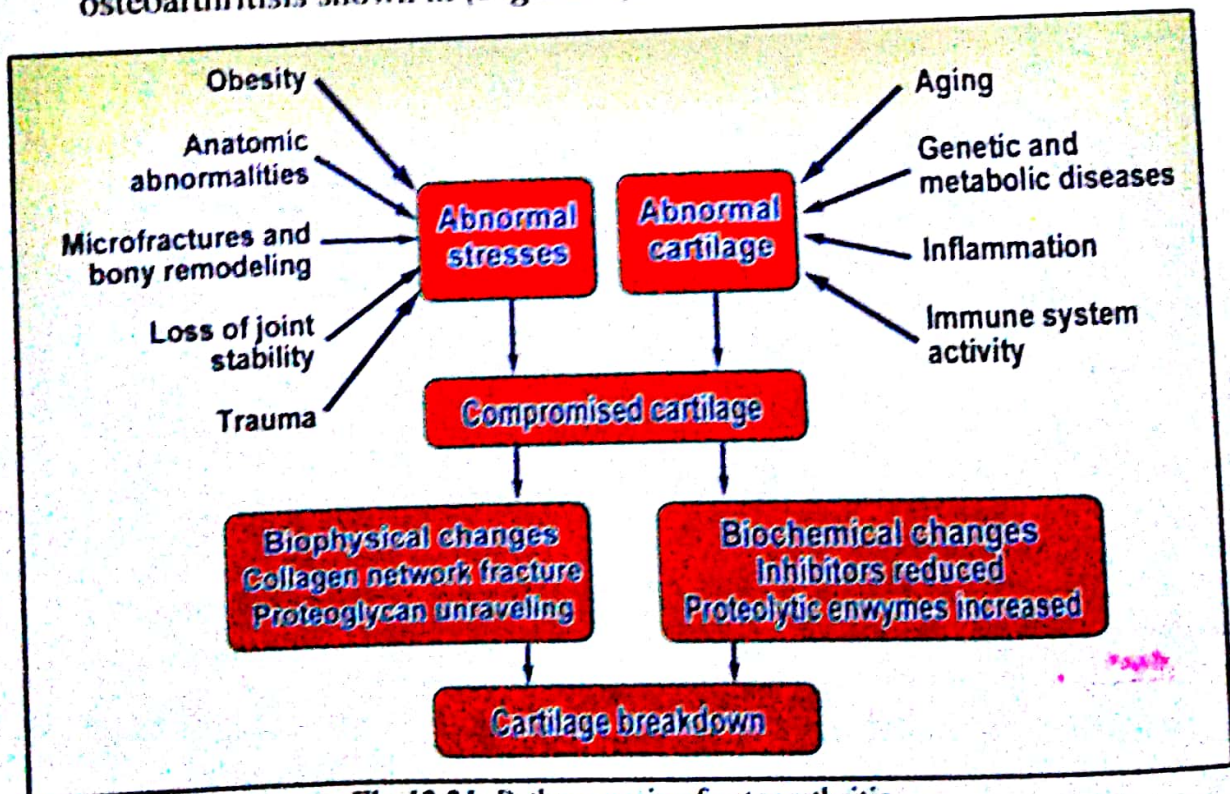


Fig.12.21; Pathogenesis of osteoarthritis

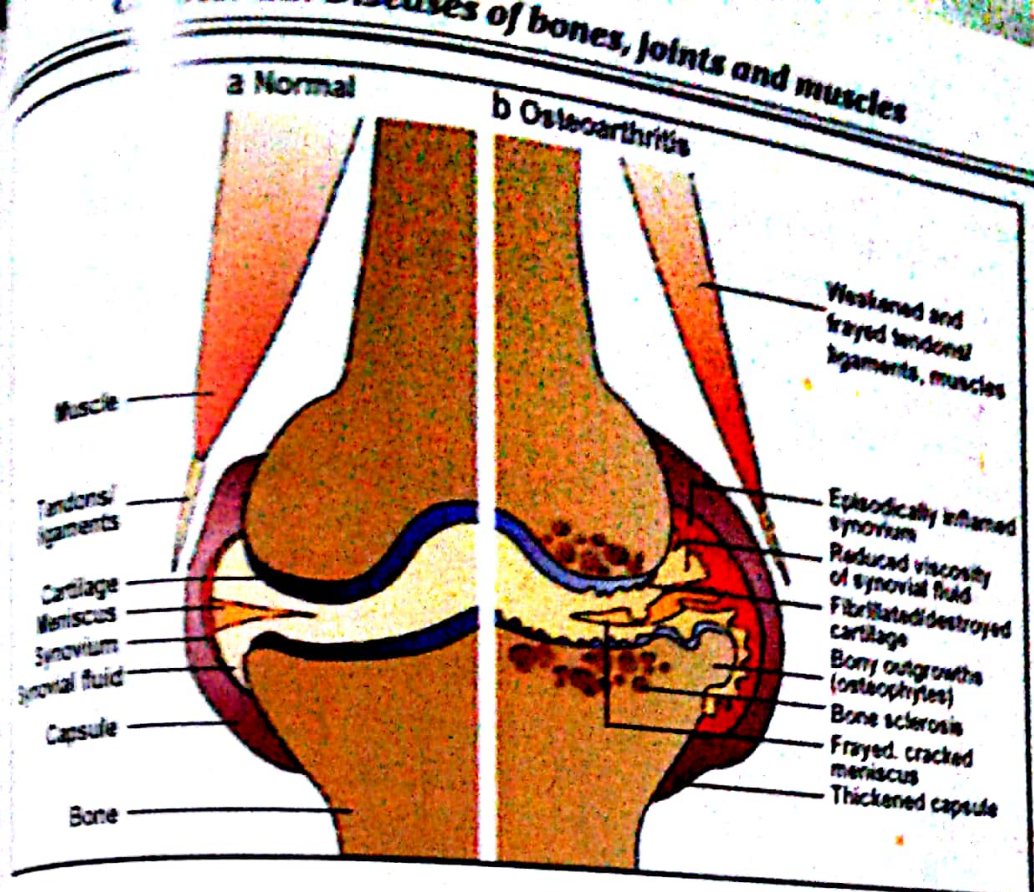


Fig.12.22; Pathology of osteoarthritis

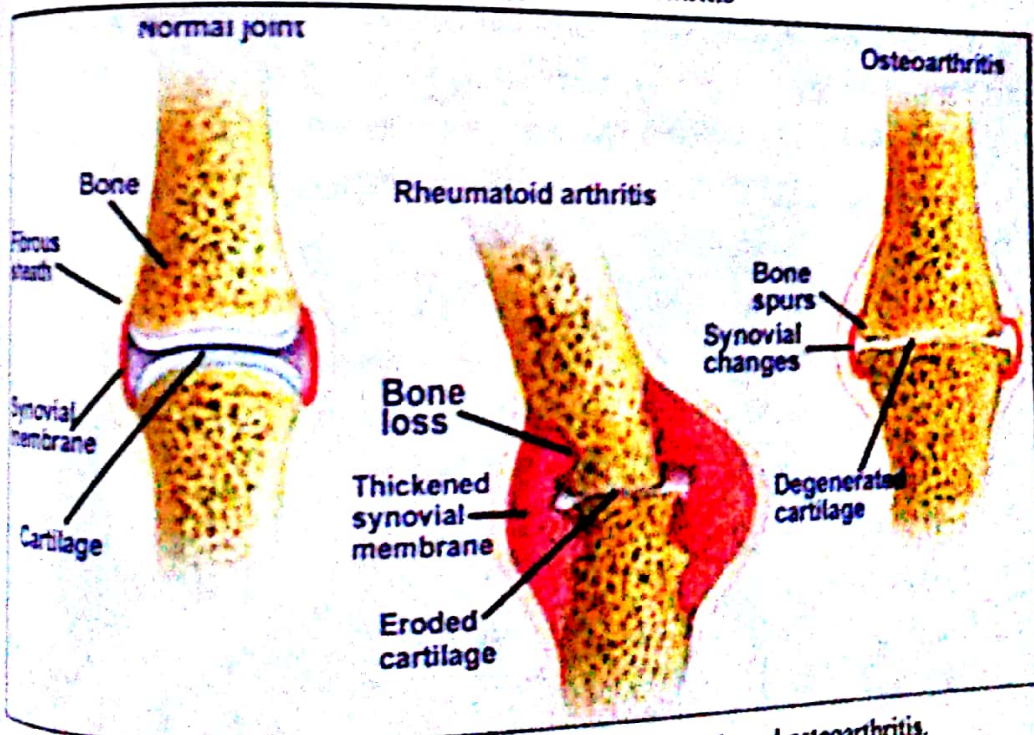


Fig.12.23: Comparison between rheumatoid arthritis and osteoarthritis.

Gout:

Gout represents a group of diseases characterized by overproduction of uric acid and with deposition of uric acid crystals in tissues and body fluids. Gout affects about 1% of the population, with a predilection for males.

Types:

- A. **Primary gout** (about 90% of cases): Designates cases in which the basic cause is unknown or (less commonly) in which the disorder is due to an inborn metabolic defect that causes hyperuricemia.
- B. **Secondary gout**: Occurs in diseases where excess breakdown of purines leads to uric acid overproduction. e.g. leukemia.

Morphology:

The major morphologic manifestations of gout are:

1. **Acute gouty arthritis:**

- It is caused by deposition of Long, slender, needle-shape sodium urate crystals in the synovial membranes of joints and periarticular tissues leading to dense neutrophilic infiltrate.
- **Affected joints:** The first metatarsophalangeal joint (big toe) is affected in 85% of cases. Elbow, knee, ankle and vertebrae may be affected.

2. **Chronic tophaceous gout:**

- It is the result of deposition of sodium urate as large amorphous masses known as tophi.
- Tophi occur commonly in the cartilage of the ear and around joints.

Microscopic: Gouty tophi appear as pale pink or brown amorphous masses surrounded by foreign body type granulomatous reaction. Marked deformity of the joint may result.

3. **Gouty nephropathy:** Refers to renal complications associated with urate deposition (tophi) or free uric acid crystals and renal calculi.

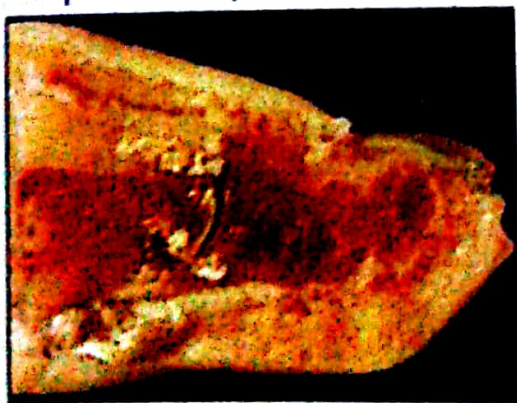


Fig.12.24: Big toe; white tophi involving the joint and soft tissues

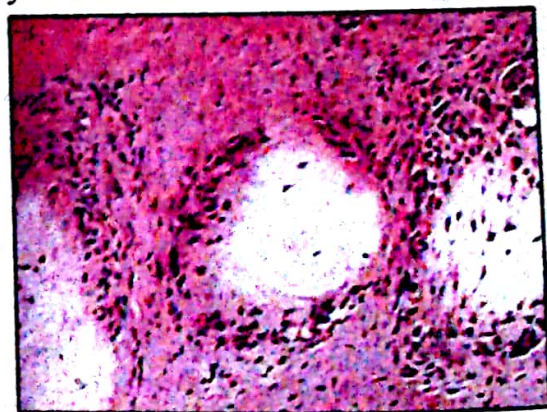


Fig.12.25: Gouty tophus, urate crystals surrounded by giant cell reaction.

Pigmented villonodular synovitis:

It is a rare condition of the synovium of joints and tendons.

Site: Finger, wrist and toes.

Gross: The synovium shows red brown folds, finger-like projection or nodules.

Microscopic: Nodules of proliferating polyhedral cells, scattered multinucleated giant cells, haemosiderin deposits, foamy macrophages and collagen.

Synovial sarcoma:

It is the malignant tumour of synovium.

Age: Third to fifth decades of life (30-50y).

Microscopic: It may be biphasic or monophasic.

1] **Biphasic lesion:** Consist of both epithelial-like and spindle cells. The epithelial cells are cuboidal to columnar and form glands or grow in solid cords. The spindle cells are arranged in densely cellular fascicles that surround the epithelial-like cells.

2] **Monophasic synovial sarcoma:** are composed of spindle or, rarely epithelial cells only. Calcified bodies could be seen.

Diseases of skeletal muscles

Disorders of neuromuscular junction:

They manifest with weakness that often affects facial and extraocular muscles and may show marked fluctuation in severity.

1- Myasthenia gravis:

- An autoimmune disorder of neuromuscular transmission characterized by progressive muscle weakness.
- Females are affected more than males.
- It occurs in association with thymic hyperplasia or thymomas.

Pathogenesis: There are autoantibodies against the acetylcholine receptor of the neuromuscular junction.

Clinical:

- Muscle weakness predominantly affecting the facial muscles.
- Extraocular muscle weakness leading to ptosis and diplopia.
- Respiratory distress due to weakness of respiratory muscles which may be the cause of death.

2- Lambert-Eaton syndrome:

- A rare autoimmune disorder of neuromuscular transmission.
- It often arises as a paraneoplastic disorder, in patients with small cell lung carcinoma.

Inherited disorders of skeletal muscles:

- 1- **Muscular dystrophies:** are inherited diseases that result in progressive muscle injury in patients who usually appear normal at birth.

- 2- *Congenital muscular dystrophies*; are progressive, early-onset diseases. Some are also associated with central nervous system manifestations
- 3- *Congenital myopathies*; they often have a perinatal or early childhood presentation and result in relatively static deficits.

Muscular dystrophy:

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are the two most important disease manifestations linked to mutations in the dystrophin gene.

a- Duschenne muscular dystrophy:

The commonest and most severe type of all inherited dystrophies.

Inheritance: It is an x-linked recessive disease.

Pathogenesis:

- The protein product, dystrophin, is a component of the sarcolemma.
- In DMD there is absence of dystrophin (component of the sarcolemma) leading to dysfunction of the sarcolemma with influx of excessive calcium ions.

Clinical presentation:

- Affected boys present around the age of 5 years.
- There is progressive muscular weakness, waddling gait and inability to rise from the ground, eventually, they become confined to wheel chair.
- Death occurs in their twenties due to respiratory failure, pneumonia or cardiac arrhythmia.

Microscopic:

- Marked variation in fiber size.
- Degeneration, necrosis and regeneration of muscle fibers.
- Replacement of muscle fibers by fat and fibrous tissue (**Fig.12.26**).
- Immunostaining reveal absence of dystrophin protein.

b- Becker Muscular Dystrophy:

An x-linked recessive inherited dystrophy.

It differs from Duschenne muscular dystrophy as follows:

- Less common and less severe.
- More slowly progressive.
- Appears at a later age (late childhood or early adolescence).

Acquired disorders of skeletal muscles:

1- Inflammatory myopathies:

a- Polymyositis:

It is an autoimmune disorder associated with increased expression of MHC class I molecules on myofibrils and predominantly endomysial inflammatory infiltrates containing CD8+ cytotoxic T cells.

It occurs in adults.

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Clinical presentation: Bilateral proximal muscle weakness.

Microscopic:

- Infiltration of muscle by lymphocytes.
- Muscle fibrils show degeneration and regeneration.

b. Dermatomyositis:

- It is the most common inflammatory myopathy in children.
- In adults, it can manifest as a paraneoplastic disorder.
- In both contexts, it is believed to have an autoimmune basis.

Clinical presentation: Skin rash and bilateral proximal muscle weakness.

Microscopic:

- Perivascular mononuclear cell infiltrates.
- Myofibrils damage in a paraseptal or perifascicular pattern.

c. Inclusion body myositis:

It is the most common inflammatory myopathy in patients over 60.

Clinical presentation: There is asymmetrical distal muscle weakness.

Microscopic: Myofibrils show rimmed vacuoles with basophilic granules and amyloid.

2. Toxic myopathy:

Thyrotoxic myopathy (in thyrotoxicosis), ethanol and drug myopathies.

Tumours of skeletal muscles

Benign tumours:

Rhabdomyoma:

- A rare benign tumour of striated muscle.
- May occur in the heart, tongue or vagina.
- Cardiac rhabdomyoma may be associated with tuberous sclerosis.

Malignant tumours:

Rhabdomyosarcoma:

- The most common soft tissue sarcoma of childhood and adolescence, usually appearing before the age of 20.
- Most common in head and neck or genitourinary tract.

Histologic types:

1. **Embryonal rhabdomyosarcoma:** Tumour arising from the bladder or vagina in infants and young children are known as (sarcoma botryoides).
2. **Alveolar variant:** Common in early to mid-teens but all ages affected.
3. **Pleomorphic variant:** Usually in patients over 50 years.

Sarcoma botryoides: Appears as soft, gelatinous, grapelike masses.

Chapter 12: Diseases of bones, joints and muscles

- Alveolar and pleomorphic variants: are poorly defined, infiltrating tan - white masses.

Microscopic:

- The rhabdomyoblast is the diagnostic cell in all types, it has granular eosinophilic cytoplasm, may be round or elongated (tadpole or strap cells) and may contain cross-striations visible by light microscopy.

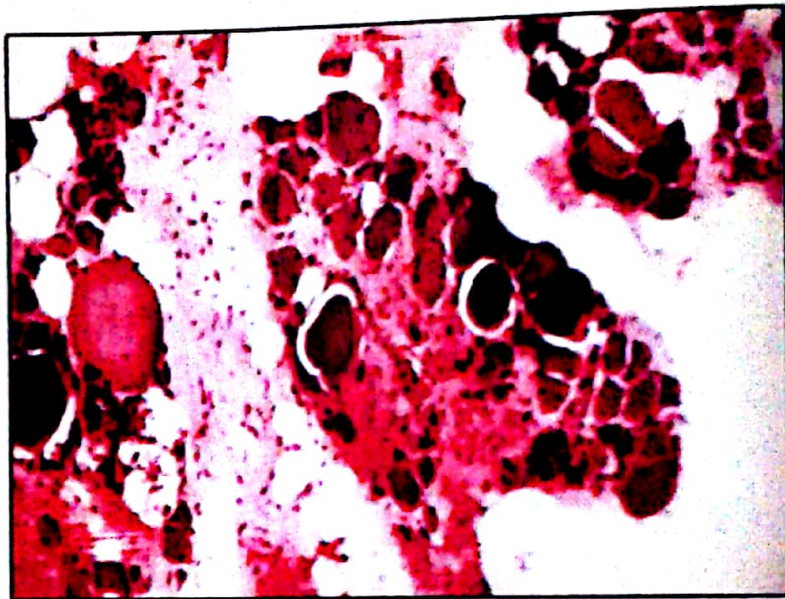


Fig.12.26: Duchenne muscle dystrophy

SUMMARY

Diseases of Bone:

Congenital Diseases of Bone:

Achondroplasia and osteogenesis imperfecta.

Osteopetrosis: Results from decreased bone mass

postmenopausal osteoporosis and

Paget disease: May result from a paramyxovirus infection with excessive osteoclast activity, followed by unsound-osteoblast deposition of bone.

Osteomyelitis: Acute haematogenous osteomyelitis. Chronic nonspecific and chronic specific TB osteomyelitis (Pott's disease)

Hyperparathyroidism: Primary or secondary leading to brown tumor or osteitis fibrosa cystica.

Bone Tumors:

Bone forming tumours:

Osteoid osteoma, Osteochondroma and Osteosarcoma (The commonest primary malignant tumour of bone of high-grade malignancy, produces osteoid matrix).

Cartilage forming tumours:

Chondroma. Osteochondroma and chondrosarcoma.

Myelogenic tumours: Plasma cell myeloma and Ewing's sarcoma.

Lymphomas:

Giant cell tumour- Composed of neoplastic mononuclear cells and reactive osteoclast-like giant cells, typically occupying long bone epiphyses.

Diseases of Joints:

Osteoarthritis: Is a primary degenerative disorder of articular cartilage with matrix breakdown exceeding synthesis. Inflammation is secondary.

Rheumatoid arthritis: A non suppurative proliferative synovitis producing permanent injury and deformity.

Gout. Increased circulating levels of uric acid can lead acute gouty arthritis, chronic tophaceous gout and gouty nephropathy.

Diseases of skeletal muscles:

Disorders of neuromuscular junction: Myasthenia Gravis

Muscular dystrophy: Duchenne and Becker muscular dystrophies.

Acquired disorders of skeletal muscles: Polymyositis, dermatomyositis,

inclusion body myositis and toxic myopathy

Tumours of skeletal muscles: Rhabdomyoma and rhabdomyosarcoma

Chapter 13

Intended Learning Outcomes (ILOs):

By the end of this unit the students will be able to:

- 1.1 Define cerebral edema and state its different types.
- 1.2 Define hydrocephalus and enumerate its causes and effects.
- 1.3 Describe stroke and differentiate it from transient ischemic attacks.
- 1.4 Define cerebral infarction, enumerate its sites and differentiate between small and large cerebral infarcts.
- 1.5 Identify cerebral aneurysm and describe its different types.
- 1.6 Describe vascular malformation.
- 1.7 Recognize spontaneous (Non traumatic) hemorrhage and its different causes.
- 1.8 Describe traumatic vascular injury and enumerate its types.
- 1.9 Recognize different infections of CNS.
- 1.10 Define acute pyogenic meningitis, list its causes in different age groups and its complications.
- 1.11 Identify viral (aseptic) meningitis and chronic meningitis.
- 1.12 Describe viral infections of CNS including acute anterior poliomyelitis, rabies and human immunodeficiency virus 1 (HIV-1).
- 1.13 Identify different causes of fungal encephalitis.
- 1.14 Recognize the main characteristics of demyelinating diseases.
- 1.15 Define multiple sclerosis and describe its manifestations.
- 1.16 Recognize Alzheimer's disease and describe its characteristic features.
- 1.17 Grade astrocytomas into four different grades (Grade I- IV) and identify the characteristics of each.
- 1.18 Describe oligodendrogliomas, ependymomas and medulloblastomas and their characteristic microscopic features.
- 1.19 Define meningioma and describe its different types.
- 1.20 Recognize metastatic CNS tumours.
- 1.21 Describe nerve sheath tumours including neurilemmoma and neurofibroma.
- 1.22 Define peripheral neuropathy and enumerate its types.
- 1.23 Analyze and diagnose a pathologic condition based on a given clinical, radiologic data and/or laboratory findings.

DISEASES OF THE NERVOUS SYSTEM

Cerebral edema

Definition: Cerebral edema is the accumulation of excess fluid within the brain parenchyma.

Pathogenesis: There are two underlying mechanisms for the development of cerebral edema that often occur together particularly when there is generalized injury.

Vasogenic edema

- Occurs when the integrity of the normal blood-brain barrier is disrupted with subsequent increase in the vascular permeability.
- Can be either localized adjacent to inflammation or tumors or generalized.

Cytotoxic edema

- An increase in intracellular fluid secondary to neuronal, glial, or endothelial cell membrane injury
- e.g. generalized hypoxic/ischemic insult or with exposure to some toxins.

Gross:

- The edematous brain is softer than normal and often appears to "overflow" the cranial vault.
- In generalized edema the gyri are flattened as a result of compression of the expanding brain by the dura mater and inner surface of the skull, the intervening sulci are narrowed and the ventricular cavities are compressed (Fig. 13. 1).

Hydrocephalus

Definition: Accumulation of excessive CSF within the ventricular system.

Pathogenesis: The balance between CSF generation and resorption keeps the volume of this fluid stable.

Normal CSF pathway (Fig.13.2):

1. CSF is formed in the lateral ventricles by the choroid plexus then passes along the foramen of Monro to 3rd ventricle and through aqueduct of Sylvius to 4th ventricle, then through foramina of Luschka and Magendie to subarachnoid space.
2. CSF is then absorbed by arachnoid villi into the superior sagittal sinus.

Causes of hydrocephalus:

Impaired flow

- Obstacle to the flow of CSF within the ventricular system
- Then a portion of the ventricles enlarges.
- This is *noncommunicating hydrocephalus*.
- Mostly seen with masses at the foramen of Monro or aqueduct of Sylvius.

Impaired resorption of CSF

- *Communicating hydrocephalus*. All the ventricular system is enlarged

Overproduction of CSF

- Rare instances (e.g., tumors of the choroid plexus).

Effects:

- When hydrocephalus develops in infancy before closure of the cranial sutures, there is enlargement of the head (Fig.11.3).
 - a. Hydrocephalus developing after fusion of the sutures, is associated with expansion of the ventricles, increased intracranial pressure without a change in head circumference.

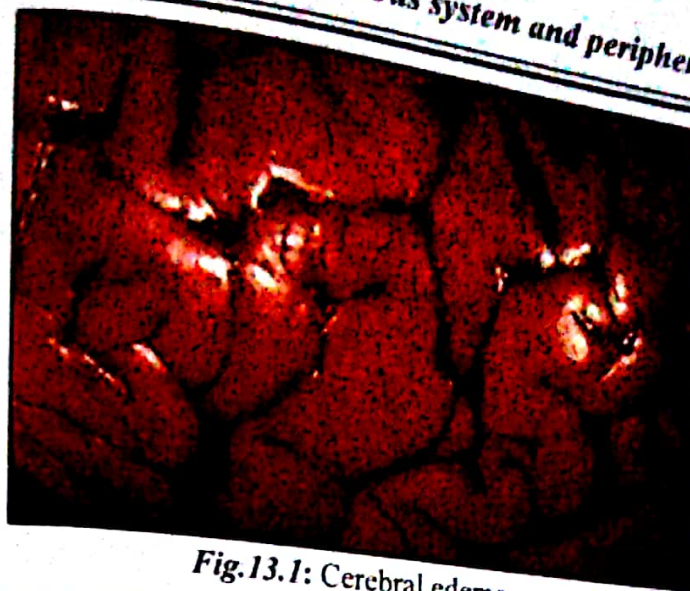


Fig.13.1: Cerebral edema

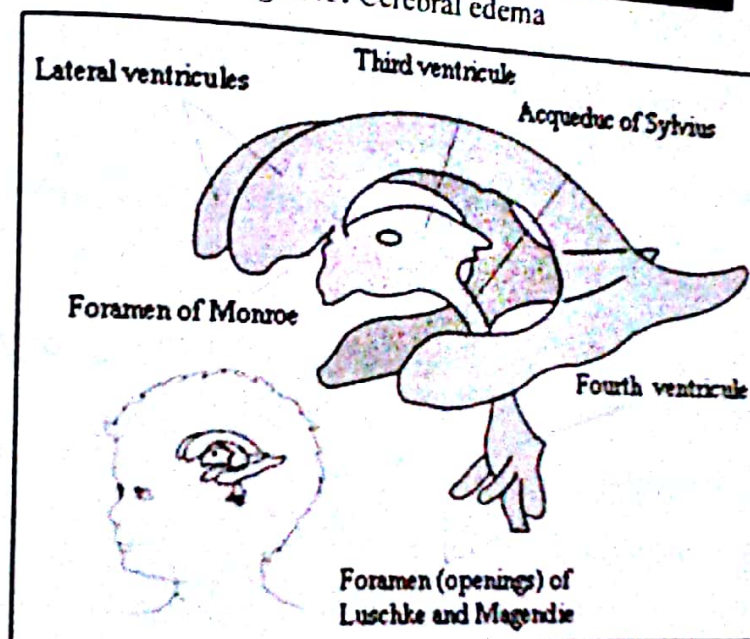


Fig.13. 2: The ventricular system



Fig.13.3: Hydrocephalus with increased head circumference in a 3-month-old child

Cerebrovascular diseases

The term *cerebrovascular disease* denotes any abnormality of the brain caused by a pathologic process involving blood vessels (Thrombosis, embolism or rupture of vessels) within the ventricular system.

"**Stroke**" is abrupt onset of focal or global neurological symptoms caused by ischemia or hemorrhage with symptoms more than 24 hours.

If symptoms resolve in less than 24 hours, the term *transient ischemic attack (TIA)* is applied.

I- Cerebral Infarction:

Causes:

1. **Arterial occlusion:** mainly due to atherosclerosis with thrombosis of internal carotid artery, cerebral arteries, vertebral and basilar arteries.
2. **Embolism from left side of heart.**
3. **Venous thrombosis associated with pregnancy and oral contraceptives.**

NB:-The commonest sites of thrombosis are; basal ganglia, internal cortex and cerebral cortex.

- Cerebral Infarction is an example of *liquefactive necrosis*, it is changed into a fluid filled cavity surrounded by glial tissue (*Fig.13.4*).

II- Cerebral aneurysm:

1. Congenital (Berry aneurysm):

- ⊛ Affecting the blood vessels around circle of Willis (*Fig.13.5*).
- ⊛ Usually multiple saccular aneurysms and if they rupture, they cause subarachnoid haemorrhage.
- ⊛ Although referred to as congenital, they are not present at birth and develop over time.
- ⊛ Associated conditions: *Polycystic kidney disease* (autosomal dominant).

Aetiology:

- Congenital defects of the media at the arterial bifurcations.
- Focal destruction of the internal elastic membrane resulting from hemodynamic alterations.
- Abnormalities in specific collagen subsets.

2. Mycotic:

- ❑ Due to *subacute bacterial endocarditis* or *polyarteritis nodosa*.
- ❑ It occurs when the wall of an artery is weakened by mild infection.
- ❑ Commonest site is branches of middle cerebral artery.

3. **Atherosclerotic:**

- ☐ It occurs due to cerebral atherosclerosis.
- ☐ It is fusiform in shape.
- ☐ Sites: Internal carotid and basilar arteries.

Effects of cerebral aneurysms:

1. Increased intracranial tension.
2. Rupture: subarachnoid haemorrhage.
3. Hydrocephalus.
4. Thrombosis and calcification.

III. Vascular malformation:

A. Arteriovenous malformation (AVM):

- AVM is admixture of arteries, veins and intermediate-sized vessels.
- Accounts for 1.5 - 4% of all brain masses.
- Common in males between 10 - 30 years.
- Middle cerebral artery distribution is the most common site.
- AVM is the most common vascular malformation associated with subarachnoid hemorrhage.

B. Cavernous malformation (Cavernous angioma):

- Large, sinusoidal-type vessels.
- Slight male predominance, most in young adults.

C. Capillary telangiectasia:

- Capillary-sized vessels separated by normal neural parenchyma.

IV. Spontaneous (Non-traumatic) Hemorrhage:

- Accounts for 10-20% of all strokes.
- More common in males.
- **Location:** Basal ganglia and thalamus (60%), lobar-cerebral (20%), cerebellum (13%) and pons (7%).

Causes:

1. **Hypertension:** Is the most common cause of non-traumatic hemorrhage due to:
 - ☐ Hyaline arteriolar sclerosis makes the arteriolar walls weaker than normal vessels and more vulnerable to rupture.
 - ☐ The development of minute aneurysms in cerebral vessels (**Charcot-Bouchard microaneurysms**).

2- Other causes:

- Ruptured Berry (saccular) aneurysm.
- Vascular malformation.
- Neoplasms.
- Blood dyscrasias, e.g. sickle-cell anemia.
- Vasculitis.

Morphology:

1. Petechial: Multiple small haemorrhages in brain substance follows septicaemia, haemorrhagic blood diseases and vitamin-B deficiency.
2. Massive: Extensive area of haemorrhage with destruction of brain tissue.

Effects:

1. Hemiplegia.
2. Increased intracranial tension.
3. Compression of brain stem and death due to tentorial herniation.

V. Traumatic Vascular Injury:

1. Extradural haemorrhage: Between dura and skull bones. It is due to trauma of middle meningeal artery.
2. Subdural: Between dura and arachnoid. It is due to trauma of cortical veins.
3. Subarachnoid: In subarachnoid space. It is due to trauma or spontaneous rupture of cerebral aneurysm.

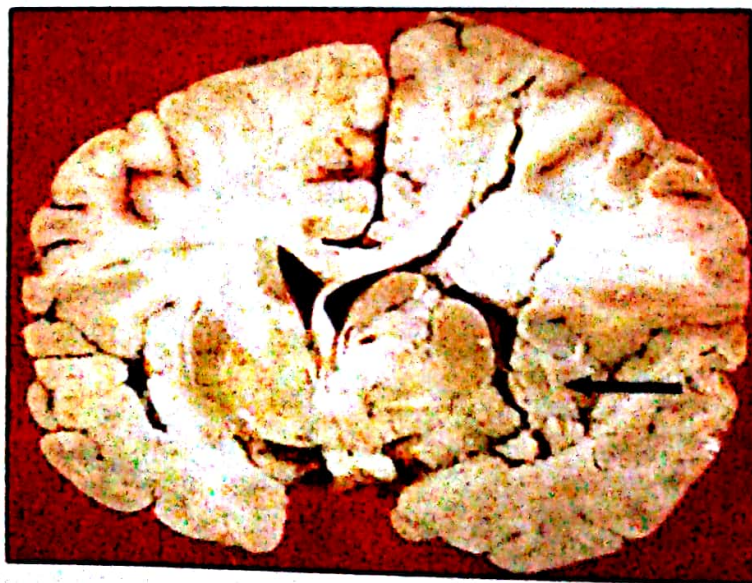


Fig.13.4: Acute infarct; note swelling and early disintegration of the infarcted area.

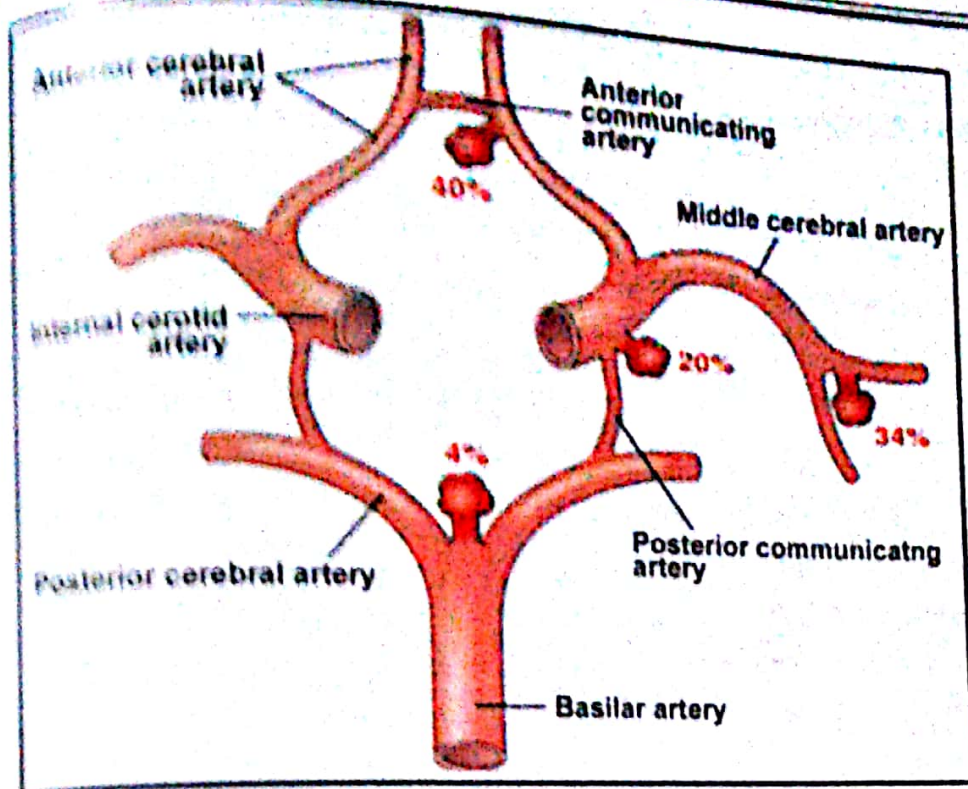


Fig.13.4: Sites of Berry aneurysms

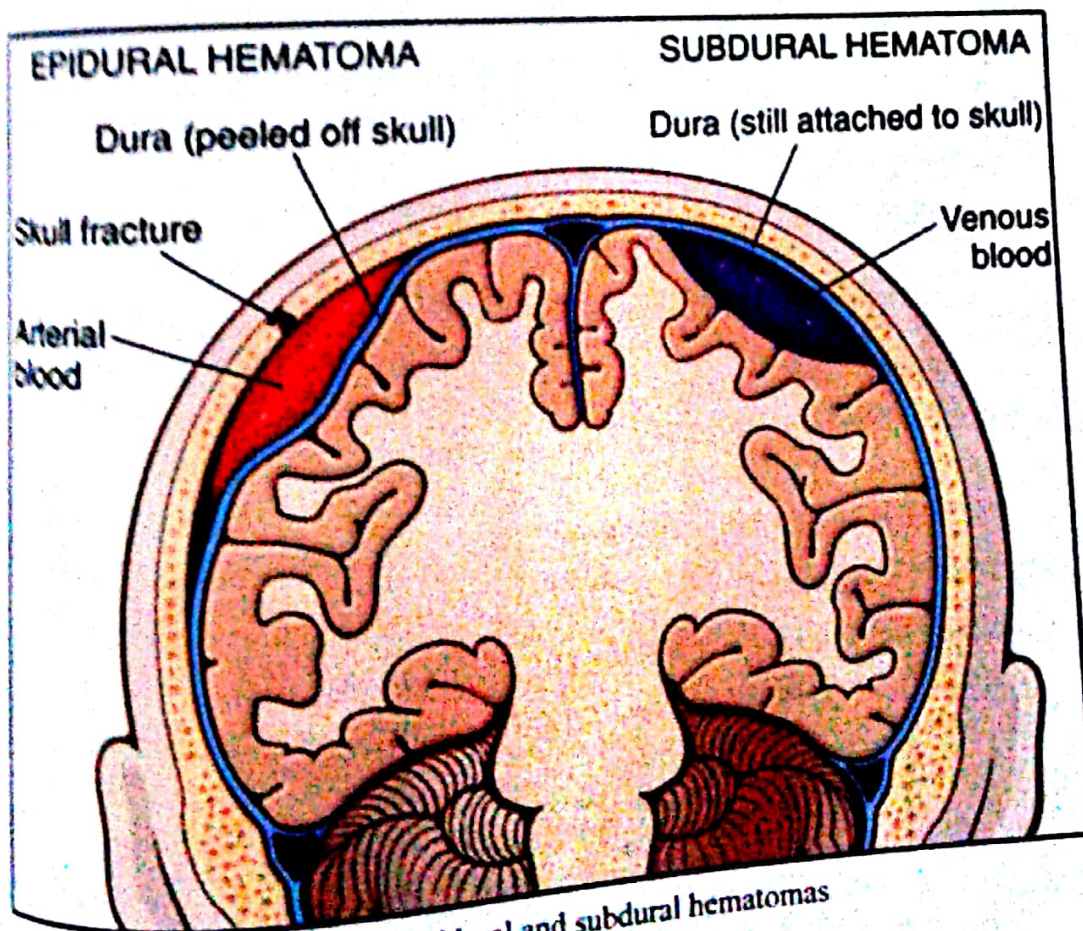


Fig.13.5: Epidural and subdural hematomas

Infections of CNS

Routes of entry:

Hematogenous spread

- Via the arterial blood supply is the most common means of entry.
- Retrograde venous spread, through the anastomoses between veins of the face and the venous sinuses of the skull.

Direct implantation

- Almost post-traumatic.
- Rarely iatrogenic, as when microbes are introduced with a lumbar puncture needle.

Local extension.

- Infection may originate in: air sinuses, an infected tooth, a surgical site in the cranium or spine, or from a
- Congenital malformation, as meningocele.

Peripheral nerves

- Is the path of entry of a few pathogens, in particular viruses, such as rabies and herpes zoster.

I- Epidural and subdural infections:

- These spaces can be involved with bacterial or fungal infections, usually as a consequence of direct local spread e.g., osteomyelitis.
- Infections of the skull or air sinuses may also spread to the subdural space, producing subdural empyema.

Meningitis:

It is inflammation of the leptomeninges and CSF within the subarachnoid space.

Causes

infectious meningitis:

- *Acute pyogenic* (usually bacterial).
- *Aseptic* (usually viral).
- *Chronic* (usually tuberculous, spirochetal, or cryptococcal)

chemical meningitis:

- In response to a nonbacterial irritant introduced into the subarachnoid space.

A. Acute pyogenic meningitis:

Causative organisms:

- In neonates: Escherichia coli and group β streptococci.
- In elderly: Streptococcus pneumoniae.
- Among adolescents and in young adults: Neisseria meningitidis.

Pathogenesis:

- Usually droplet infection via respiratory tract followed by septicemia as in case of meningococcal meningitis and haemophilus influenza.
- Via skin as in neonatal meningitis.
- By direct spread from otitis media or paranasal sinuses.

Gross:

- ☐ A suppurative exudate is evident within the leptomeninges over the surface of the brain (**Fig.13.6**).
- ☐ The meningeal vessels are engorged and prominent.
- ☐ CSF is mixed with pus.

Microscopic:

- ☐ Meningeal vessels are congested and dilated.
- ☐ The subarachnoid space is filled with fibrin, neutrophils, pus cells and histiocytes.

CSF changes:

- An increased CSF pressure.
- Abundant neutrophils and bacteria.
- Elevated protein content.
- Reduced glucose content.

Effects and complications:

Local:

- Increased intracranial tension.
- Meningeal fibrosis may cause obstruction of the foramina of Lushcka and Magendie, leading to hydrocephalus in children and manifestations of increased ICT in adults with damage of cranial nerves; mainly III, IV, VI leading to diplopia, squint and ptosis.
- Encephalitis.
- Thrombosis of blood vessels.

General:

- Septicemia leads to:
 - Infective endocarditis or
 - Acute adrenal insufficiency "Waterhouse - Friedrichsen Syndrome".

B- Viral (aseptic) meningitis:

- The clinical course is less fulminant than in pyogenic meningitis.
- It is usually self-limiting and often treated symptomatically.
- The CSF shows:
 - An increased number of lymphocytes.
 - The protein elevation is only moderate.
 - Glucose content is nearly always normal.
 - In most cases, the virus can be identified, commonly enterovirus.

Gross: No distinctive macroscopic characteristics.

Microscopic: There is mild to moderate infiltration of the leptomeninges with lymphocytes.

C- Chronic meningitis:

1- Tuberculous meningitis:

It is a cause of arachnoid fibrosis which may produce hydrocephalus.

- **CSF:**
 - Moderate increase in mononuclear cells.
 - Protein level is elevated.
 - Glucose content is moderately reduced or normal.
- Infection with *Mycobacterium tuberculosis* may also result in a well-circumscribed intraparenchymal mass (*tuberculoma*), which may be associated with meningitis.

2- Neurosyphilis:

It occurs in the tertiary stage of syphilis in the form of:

- a- Meningiovascular lesions; meningeal vessels show either diffuse reaction or gumma leading to cerebral ischemia.
- b- Tabes dorsalis degeneration of posterior column of spinal cord causing gait abnormalities.
- c- General paralysis of the insane "GPI": Meningioencephalitis with cortical atrophy and neuronal loss there is loss of mental and physical functions, mood alterations ending in dementia.

II- Parenchymal infections:

A- Brain abscess:

Causative organisms:

Streptococci, Staphylococci, Pneumococci, E.coli and B.pyocyaneus.

Mode of infection:

1. Direct implantation:
 - a- Traumatic.
 - b- Local extension: e.g. suppurative mastoiditis or acute suppurative otitis media.
2. Haematogenous: (systemic pyaemia):
 - a- Acute bacterial endocarditis.
 - b- Suppurative lung diseases via vertebral system of veins.

Sites:

- ☐ The temporo-parietal area or the cerebellum if complicating middle ear disease.
- ☐ The frontal lobe if complicating lung infection, sinusitis or fractures.
- ☐ Multiple small abscesses in case of systemic pyaemia.

Microscopic:

- Acute abscess appears as an irregular area of liquefactive necrosis surrounded by a zone of congestion.
- Chronic abscess has a smooth fibrous tissue capsule surrounded by a zone of reactive gliosis.

Clinical:

- Progressive focal deficits.
- The CSF white cell count and protein level are raised, but the glucose content is normal.
- Increased ICT and progressive herniation which may be fatal.
- Abscess rupture can lead to ventriculitis, meningitis and venous sinus thrombosis.

B- Viral encephalitis:

It is infection of the brain that is invariably associated with meningeal inflammation (*meningoencephalitis*).

1- Viral infections:

- The most characteristic histologic features are perivascular and parenchymal mononuclear cell infiltrates, microglial nodules and neuronophagia.
- Certain viruses may form *inclusion bodies*.

(a) Acute poliomyelitis:

- It is an acute viral infection of the grey matter of the anterior horn cells (AHC) of the lumbar and cervical regions of spinal cord.
- It usually affects infants and young children, but may occur in adults.

Mode of infection:

- Infection occurs by ingestion of contaminated food and drinks.

Microscopic:

- Degeneration and necrosis of AHC. Congestion with perivascular cellular infiltrate consisting of PNL and lymphocytes.
- The motor nerves show demyelination with degeneration.

Clinical:

1. Prodromal stage: With pyrexia, malaise, headache, nausea, vomiting and sore throat. This may subside or progress to.
2. Pre-paralytic stage: With pyrexia, stiff neck, limb and back pains and signs of meningeal irritation.
3. Paralytic stage: With flaccid paralysis of the muscles supplied by affected nerve cells.

(b) Rabies:

- ❑ Transmitted by the bite of a rabid animal (dog, cats) and the virus ascends to CNS along the peripheral nerves from the wound site.
- ❑ Causes extraordinary CNS excitability, hydrophobia, flaccid paralysis and death ensues from respiratory center failure.
- ❑ Widespread neuronal necrosis and inflammation, most severe in basal ganglia, midbrain and medulla.
- ❑ **NEGRI Bodies** (intracytoplasmic eosinophilic inclusions) are found in hippocampal pyramidal cells and purkinje cells.

(c) Human immunodeficiency virus 1 (HIV-1):

- ❑ Up to 60% of patients with AIDS develop neurologic symptoms and neuropathologic changes have been observed in 80 - 90% of cases
- ❑ HIV can have direct effects on the nervous system as well as setting the stage for opportunistic infections or tumors that can involve the nervous system.
- ❑ Patterns of direct injury to the brain include:
 - a- HIV -1 aseptic meningitis.
 - b- HIV-1 meningoencephalitis (AIDS dementia).
 - c- Vacuolar myelopathy.

C- Fungal encephalitis:

- *Candida albicans*, *mucormycosis* and *aspergillus fumigatus*, are the most common fungi that can cause encephalitis.

- Although most fungi invade the brain by hematogenous dissemination, direct extension may occur, particularly with *mucormycosis*, in diabetics.
- *Parenchymal invasion*, in the form of granulomas or abscesses.
- *Aspergillus* causes a widespread septic hemorrhagic infarctions due to invasion of blood vessel walls with subsequent thrombosis.

D- Other meningoencephalitis:

A wide range of other organisms can infect the nervous system and its covering e.g. toxoplasmosis, cysticercosis, amoeba and hydatid cyst.

Demyelinating diseases

These are conditions characterized by a preferential damage to myelin with relative preservation of axons.

1- Multiple sclerosis:

It is an autoimmune disorder characterized by distinct episodes of neurologic deficits separated in time, due to demyelinating white matter lesions that are separated in space.

It is more common in European countries than Orientals.

Age: 20 -40 years, common in females.

Etiology:

It is an autoimmune disease caused by a combination of environmental and genetic factors resulting in loss of tolerance to self proteins (myelin antigens).

1. A transmissible agent (virus) has been proposed but not identified yet.
2. Genetic lineage of MS susceptibility to HLA-DR2 is established

Gross (Fig.13.7a):

- It is characterized by presence of plaques of demyelination of the white matter. These plaques are perivenular and appear as irregular well demarcated grey or translucent lesions with a diameter ranging between 0.1 cm to several centimeters.
- Sites of predilections are; optic nerve, paraventricular, brain stem, spinal cord and cerebral white matter. Any area of the brain can be affected.

Microscopic (Fig.11.7b):

- Plaques show demyelination (best seen in section stained for myelin) and tangled masses of preserved axons (best seen in silver stained sections).

- Lymphocytic infiltration is present in areas of active and recent myelination.

Clinical:

1. It is characterized by episodic relapses and remissions over many years.
2. The clinical manifestations depend on the area of brain affected and include abnormalities of vision, cerebellar dysfunction, parasthesia, weakness and spinal cord dysfunctions.

Post vaccinal encephalomyelitis:

- It follows measles, small pox, chicken pox and rabies.
- There is auto-immune reaction against nervous tissue leading to demyelination and perivascular infiltration with plasma cells and lymphocytes.

Degenerating diseases

The most important of this group is:

Alzheimer's disease:

- ❑ Principal clinical manifestation is dementia.
- ❑ Usually begins after the age of 50 years.
- ❑ Gyri are narrowed and sulci widened especially in frontal, temporal and parietal lobes.

Microscopic:

1. Neurofibrillary tangles; bundles of argyrophilic paired helical filaments in neuronal cytoplasm (*Fig.13.8*).
2. Neuritic plaques.
3. Amyloid angiopathy.

Parkinsonism:

It is characterized by tremor, rigidity, bradykinesia and instability.

Parkinsonism syndrome: Occurs with diseases, drugs or toxins that selectively injure dopaminergic neurons in the substantia nigra.

Parkinson disease (PD): Is an idiopathic disease

Pathogenesis of PD:

- Most cases of PD are sporadic, both autosomal dominant and recessive forms of the disease also exist. There is a defect in α -synuclein, a protein involved in synaptic transmission.
- **Lewy body** is an inclusion containing α -synuclein.

Chapter 13: Diseases of the nervous system and peripheral nerves

Gross: Pallor of the substantia nigra and locus ceruleus.

Microscopic: Depigmented substantia nigra. Lewy bodies appear as single or multiple, intracytoplasmic, eosinophilic, round to elongated inclusions with dense core surrounded by a pale halo.

Clinical Features

- PD commonly manifests as a movement disorder.
- It progresses producing severe motor slowing over 10 to 15 years.
- Death usually is the result of inter current infection or trauma from frequent falls caused by postural instability
- Dementia (*Lewy body dementia*) arises within 1 year of the onset of motor symptoms.



Fig.13.6: Pyogenic meningitis

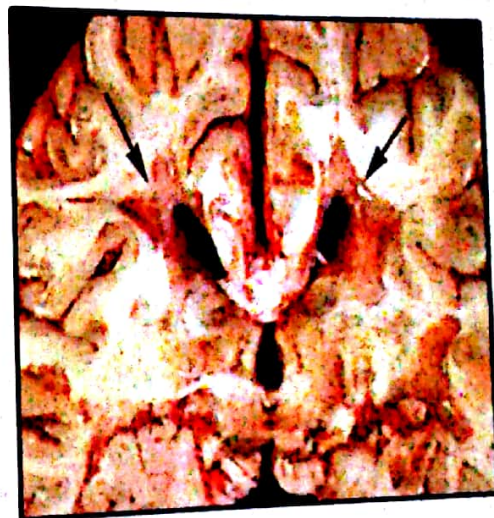


Fig.13.7a: MS, paraventricular plaques (arrow)

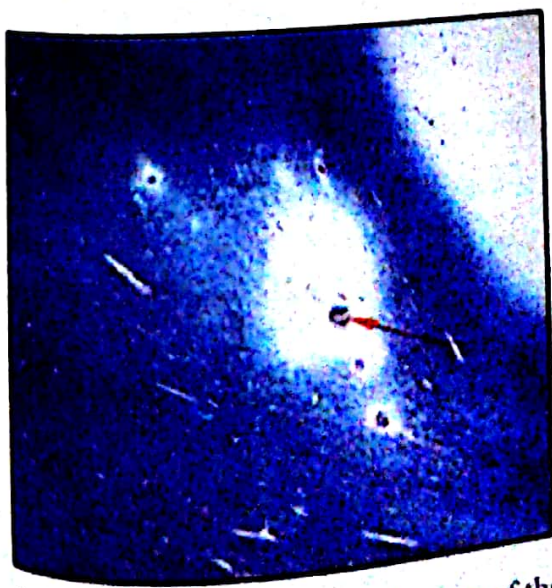


Fig.13.7b: MS; note a clear area of the lesion (myelin stain).

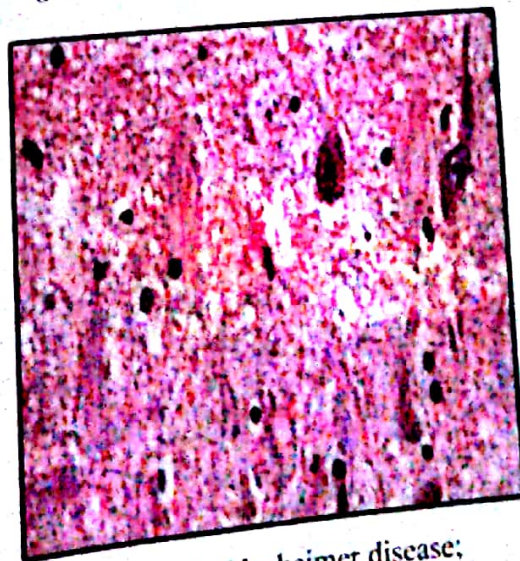


Fig.13.8: Alzheimer disease; neurofibrillary tangles

Nervous system tumours

Classification:

(1) Tumours of neuroglia (gliomas):

- ☐ Astrocytes: Astrocytoma.
- ☐ Oligodendrocytes: Oligodendroglioma.
- ☐ Ependyma.
 - Ependymoma.
 - Myxopapillary ependymoma.
 - Subependymoma.

(2) Tumours of choroid plexus:

- ☐ Choroid plexus adenoma
- ☐ Choroid plexus carcinoma

(3) Tumours of neurons: ←

- ☐ Neuroblastoma.
- ☐ Ganglioneuroblastoma.
- ☐ Ganglioneuroma.

(4) Tumours of neurons and neuroglia: Ganglioglioma.

(5) Tumours of undifferentiated cells: Medulloblastoma.

(6) Tumours of pineal cells: Pineoblastoma, pineocytoma.

(7) Tumours of meninges: Meningioma, meningeal sarcoma.

(8) Tumours of nerve sheath cells: Neurilemmoma, neurofibroma.

(9) Malformative tumours:

- ☐ Cranio-pharyngioma.
- ☐ Epidermoid cyst.
- ☐ Dermoid cyst.
- ☐ Colloid cyst.

(9) Lymphomas: primary or secondary.

(10) Metastatic tumours.

Table 13.2 WHO classification and grading of common CNS tumours, 2007

Tumour	WHO grade
<u>Astrocytomas:</u>	
Pilocytic astrocytoma.	I
Low grade fibrillary astrocytoma.	II
Anaplastic astrocytoma.	III
Glioblastoma.	IV
<u>Oligodendroglioma:</u>	
Low grade oligodendroglioma.	II
Anaplastic oligodendroglioma.	III
<u>Ependymomas</u>	
Ependymoma.	II
Anaplastic ependymoma.	III
<u>Medulloblastoma.</u>	IV
<u>Meningiomas:</u>	
Benign meningioma	I
Atypical meningioma.	II
Anaplastic meningioma.	III

Gliomas:

1- Astrocytomas:

About 80% of adult primary brain tumours, usually in cerebral hemispheres, but may occur in the cerebellum, brain stem or spinal cord.

Pathological features of WHO grades of astrocytoma (Table 13.2).

1- Pilocytic astrocytomas (Grade I):

- Occur in children and young adults.
- Pilocytic astrocytomas are relatively benign tumors (WHO grade I)
- They grow very slowly with good prognosis.

Gross:

- Usually located in the cerebellum, and in the optic nerves.
- It is often cystic, with a mural nodule in the wall of the cyst; if solid, it is usually well circumscribed.

Microscopic:

- The tumor is composed of areas with bipolar cells with long, thin "hairlike" processes that are GFAP positive.
- Rosenthal fibers, eosinophilic granular bodies and microcysts are often present (Fig.13.9).
- Necrosis and mitoses are absent.

b- Low grade fibrillary astrocytoma (Grade II):

- Are poorly defined, grey-white, infiltrative tumours that expand and distort a region of the brain.
- They show hypercellularity and minimal nuclear pleomorphism.

c- Anaplastic (Malignant) astrocytoma (Grade III):

- Show more densely cellular areas, greater nuclear pleomorphism and increased mitoses.

d. Glioblastoma (Grade IV):

The most malignant astrocytoma.

Gross: Shows a mixture of firm, white areas, soft yellow foci of necrosis, cystic change and hemorrhage (Fig.13.10).

Microscopic: It is similar to anaplastic astrocytoma with the additional features of necrosis (often with pseudo-palisading nuclei) or/and vascular proliferation (Fig.13.11a&b).

Table.13.2: Histologic criteria of WHO grades of astrocytoma

WHO Grade	WHO Designation	Histological Criteria
I	Pilocystic astrocytoma	
II	Diffuse astrocytoma	One criterion: nuclear atypia
III	Anaplastic astrocytoma	Two criteria: usually nuclear atypia and mitotic activity
IV	Glioblastoma	Three criteria: nuclear atypia, mitoses with necrosis or/and vascular proliferation.

II. Oligodendrogliomas:

Represents 5 - 15% of gliomas in middle life.

Gross: Are infiltrative tumors that form gelatinous, gray masses, and may show cysts, and calcification.

Microscopic:

Oligodendrogliomas (WHO grade II) are composed of

- Sheets of regular cells with spherical nuclei containing finely granular chromatin surrounded by a clear halo of cytoplasm (Fig 13.12).
- Calcification, present in as many as 90% of these tumors.
- Mitotic activity is usually very difficult to detect.

WHO grade III tumors show increasing cellularity, nuclear atypia, mitotic activity and presence of necrosis.

□ Oligodendrogliomas has a better prognosis than astrocytomas.

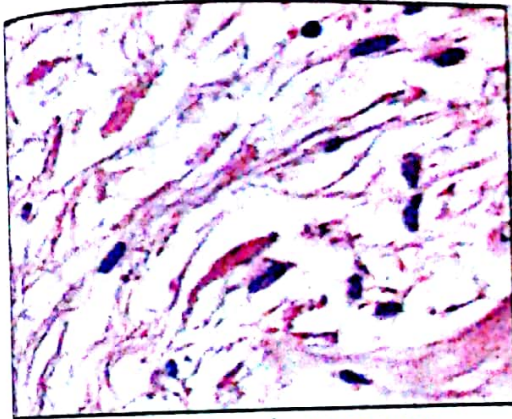


Fig.13.9: Pilocytic astrocytoma with Rosenthal fibers

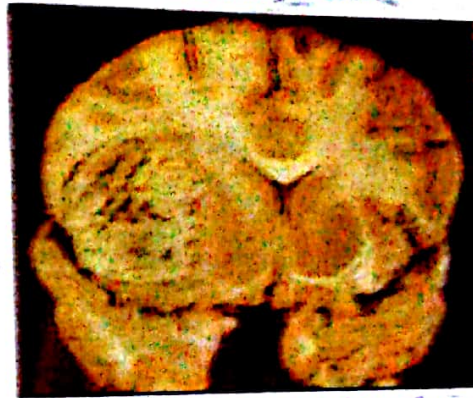


Fig.13.10: GBM, a territorial, hemorrhagic, infiltrating mass

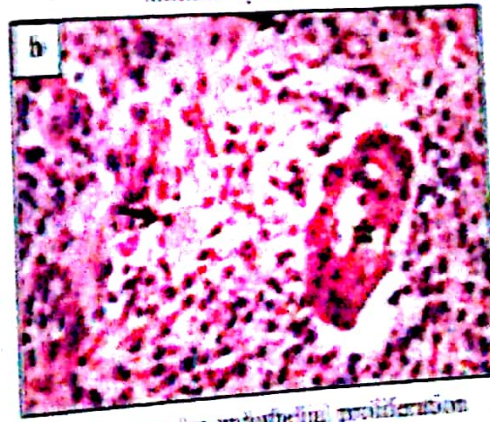
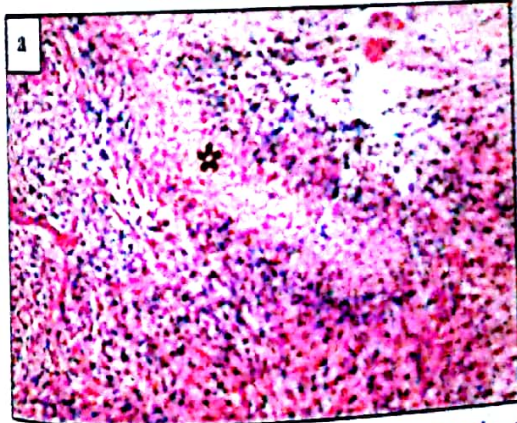


Fig.13.11: GBM; (a)Palisading necrosis. (b) Mitoses & vascular endothelial proliferation

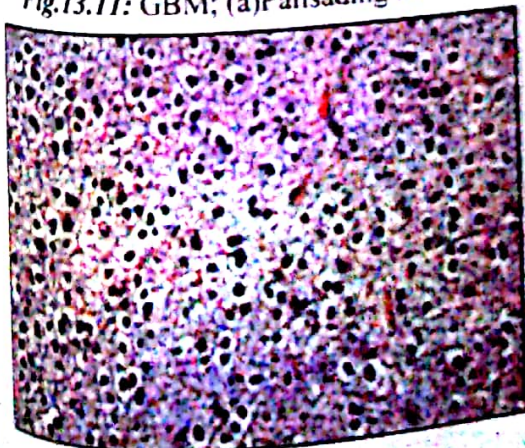


Fig.13.12: Oligodendroglioma



Fig.13.13: Ependymoma

3. Ependymoma:

- ❑ These tumours arise from the ependymal lining of the ventricular system, including the central canal of the spinal cord.
- ❑ CSF dissemination is a common finding.
- ❑ In the first two decades of life, occurs in the fourth ventricle. In the middle life, occurs in spinal cord.

Gross: Solid or papillary masses extending from the floor of the ventricle.

Microscopic: Tumour cells have regular, round-to-oval nuclei with abundant granular chromatin; they may form ependymal rosettes, or, more frequently, perivascular pseudorosettes (Fig.13.13).

Anaplastic ependymomas (WHO grade III) show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation.

Medulloblastoma:

- ❑ Comprise 20% of childhood brain tumours and occur exclusively in the cerebellum (Fig.13.14a).
- ❑ They are extremely cellular neoplasms, formed of sheets of anaplastic small cells with hyperchromatic nuclei showing abundant mitoses. Rosettes are also seen (Fig.13.14b).
- ❑ The tumour is highly malignant but radiosensitive.

Meningiomas:

- They are predominantly benign tumours of adults, usually attached to the dura and arise from the meningotheial cell of the arachnoid.
- Meningiomas may be found along any of the external surfaces of the brain as well as within the ventricular system where they arise from the stromal arachnoid cells of the choroid plexus.

Gross:

- ❑ Grow as well-defined dural-based greyish white masses with whorly cut surface that compress underlying brain but are easily separated from it (Fig.11.15a).
- ❑ Extension into the overlying bone may be present.

1- Benign meningiomas (WHO grade I):

Microscopic: There are many different histologic patterns including:

- **Syncytial**, whorled clusters of cells without visible cell membranes.
- **Fibroblastic**, with elongated cells and abundant collagen deposition.
- **Transitional**, shares features of the syncytial and fibroblastic types.
- **Psammomatous**, with numerous psammoma bodies (Fig.13.15b).

- 2- Atypical meningiomas (WHO grade II): with a higher rate of recurrence, more aggressive local growth and higher mitotic rate.
- 3- Anaplastic (malignant) meningiomas (WHO grade III) are highly aggressive tumors that resemble a high-grade sarcoma.

Prognosis of meningiomas is influenced by:

- Size and location of the lesion.
- Surgical accessibility.
- Histologic grade.

VB: The presence of brain invasion is associated with increased risk of recurrence.

Metastatic tumours:

Brain metastasis are common and are derived from melanomas or from lung, breast, kidney, stomach and colon. Meningeal involvement by metastatic neoplasms occurs frequently in patients with acute leukemia.

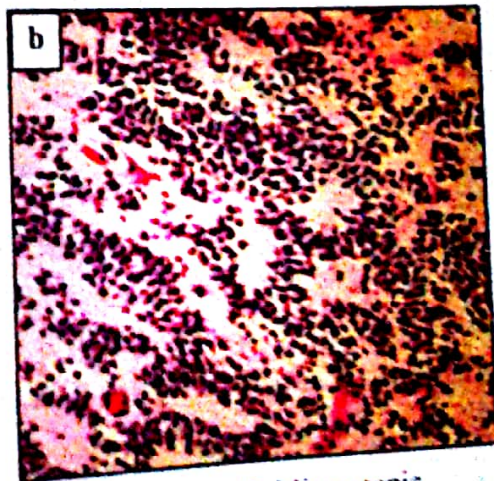
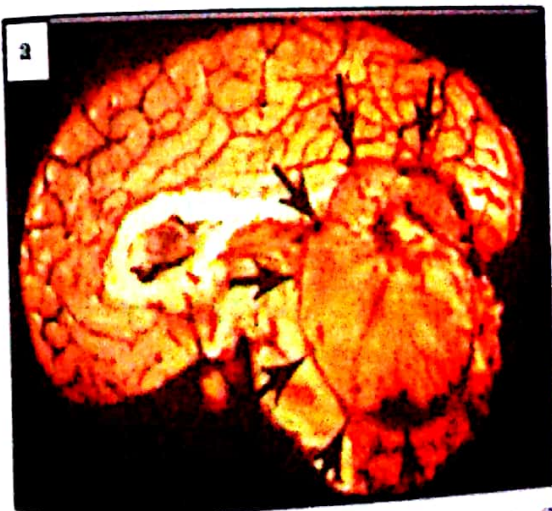


Fig.13.14: Medulloblastoma. A, Sagittal section of brain. B, Microscopic

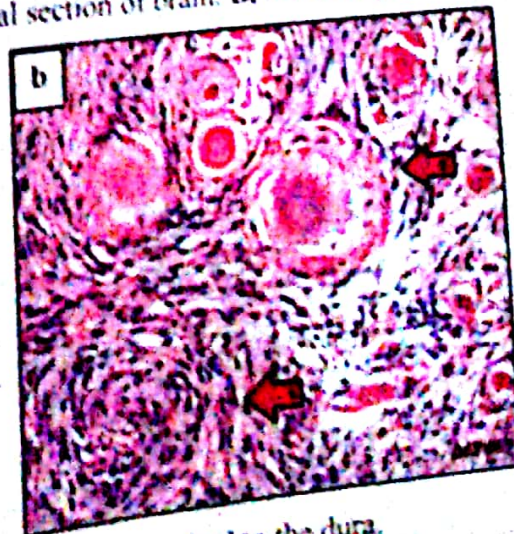
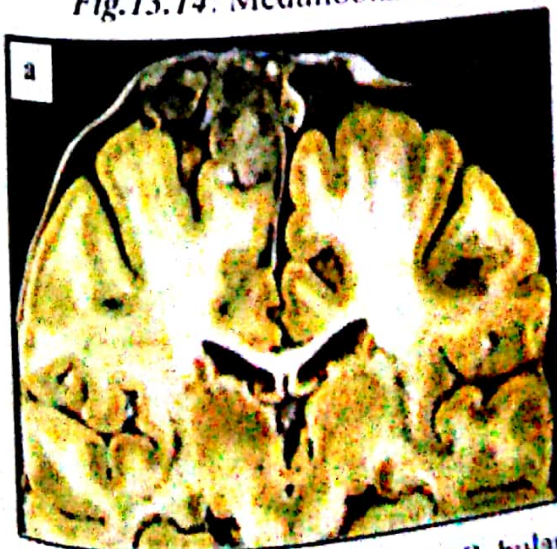


Fig.13.15: a) Parasagittal multilobular meningioma attached to the dura.
b) Meningioma with a whorled pattern of cell growth and psammoma bodies.

Peripheral nerves

Patterns of peripheral nerve injury

Most peripheral neuropathies can be subclassified as either axonal or demyelinating.

- a. **Wallerian degeneration:** Axonal degeneration is associated with secondary myelin loss. Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon.
- b. **Demyelinating neuropathies:** Are characterized by damage to Schwann cells or myelin with relative axonal sparing, resulting in abnormally slow nerve conduction velocities.

Types of peripheral neuropathies:

1- Guillain-Barré syndrome

- It is a rapidly progressive acute demyelinating disorder affecting motor axons that results in ascending weakness that may lead to death from failure of respiratory muscles over a period of only several days.
- It is triggered by an infection (*Campylobacter jejuni*, EBV, CMV, and HIV) that breaks down self-tolerance, leading to an autoimmune response.

3- Chronic inflammatory demyelinating polyneuropathy

- It is symmetric immune-mediated disorder that occurs in patients with systemic lupus erythematosus and HIV infection.
- The peripheral nerves show segments of demyelination and remyelination.

3- Diabetic peripheral neuropathy

- Diabetes is the most common cause of peripheral neuropathy.
- Distal symmetric sensorimotor polyneuropathy is the most common form of diabetic neuropathy. Sensory axons are more severely affected than motor axons, so the clinical presentation usually is dominated by paresthesias and numbness.

4-Toxic, vasculitic and inherited peripheral neuropathy.

Nerve Sheath Tumours

1. Neurilemmoma (Schwannoma):

- ☐ Benign tumours of neural crest-derived from Schwann cells, most commonly associated with vestibular branch of eighth nerve at cerebellopontine angle (vestibular schwannoma or acoustic neuroma).
- ☐ May be associated with deafness.

Gross: Schwannomas are well circumscribed, encapsulated masses, attached to nerve (Fig. 13.16a).

Microscopic: Tumours show a mixture of two growth patterns:
 Type 1: elongated cells with cytoplasmic processes arranged in fascicles with focal nuclear palisade arrangement in areas of high cellularity with little stromal matrix (Fig. 13.16b).

Type 2: less cellular tissue with stromal microcysts and myxoid changes. Cells with vacuolated cytoplasm are seen.

Malignant change is rare.

2. Neurofibroma:

- It occurs sporadically or in association with neurofibromatosis.
- It occurs in the skin and in the spinal column (intradural but extramedullary).
- The tumour is not capsulated and is composed of spindle cells in collagenized stroma.
- The tumour cells may be arranged in plexuses (plexiform neurofibroma).
- In case of neurofibromatosis the tumour appears as multiple skin nodules with skin hyperpigmentation (Cafe au lait patches).
- It is liable to malignant change.

3. Malignant peripheral nerve sheath tumour (MPNST):

A highly malignant invasive sarcoma, either de novo or from plexiform neurofibroma.

Effects of intracranial tumours:

- Local effects; e.g. hemorrhage, oedema and manifestations of increased intracranial tension.
- Herniation of brain in foramen magnum which causes central failure.
- Hydrocephalus in children.

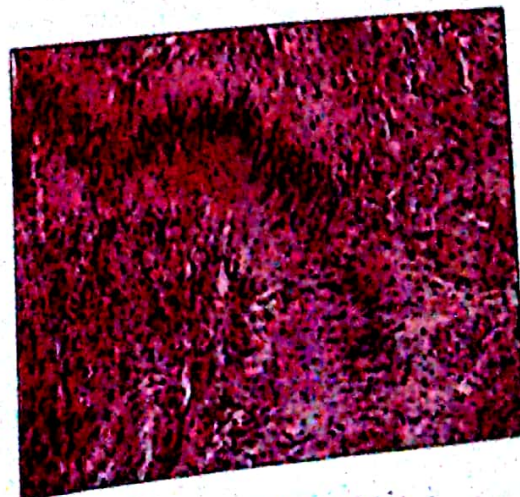
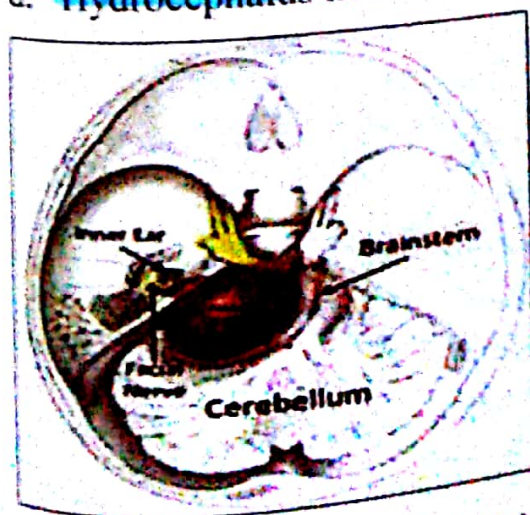


Fig. 13.16: Acoustic neuroma (Schwannoma), (a) Gross, (b) Microscopic

SUMMARY

Cerebral edema:

Types: Vasogenic edema & cytotoxic edema

Hydrocephalus: It is the accumulation of excessive CSF within the ventricular system.

Cerebro vascular lesions: Stroke, transient ischemic attack & cerebral infarction;

Cerebral aneurysm: Congenital, mycotic & atherosclerotic

Vascular Malformation: Arteriovenous malformation (AVM), cavernous malformation & papillary telangiectasia

Spontaneous (Non traumatic) Hemorrhage: The commonest cause is hypertension

Infections of CNS:

Acute pyogenic and viral meningitis;

Chronic meningitis: *Tuberculous meningitis, neurosyphilis:*

Parenchymal infections:

Viral infections: Poliomyelitis, rabies, HIV, fungal encephalitis, candida, mucor and aspergillus fumigates.

Demyelinating diseases: Multiple sclerosis.

Degenerating diseases: Alzheimer's disease.

Nervous System Tumours:

- *Gliomas:* Astrocytomas (Pilocytic astrocytomas, low grade fibrillary astrocytomas, anaplastic & glioblastoma).
Oligodendrogliomas, ependymoma & medulloblastoma.
- *Meningiomas:* Benign, atypical & anaplastic.
- *Metastatic tumours:*

Peripheral nerves:

- *Peripheral nerve injury:* Wallerian (axonal) degeneration and demyelinating neuropathies
- *Peripheral polyneuropathy.*
- *Nerve sheath tumours:* Neurilemmoma & neurofibroma

Chapter 14

Intended Learning Outcomes (ILOs):

By the end of this chapter students should be able to:

- ❏ Define urticaria, explain its pathogenesis and describe its pathologic features.
- ❏ Define psoriasis, explain its pathogenesis and describe its pathological features.
- ❏ Compare between the acute eczematous dermatitis and erythema multiforme.
- ❏ Identify types of chronic inflammatory dermatosis and describe pathological features of each.
- ❏ Describe the pathological feature of verruca vulgaris.
- ❏ Compare and contrast different types of blistering disorders.
- ❏ Identify seborrheic keratosis and describe its pathologic features.
- ❏ Define pemphigus vulgaris, explain its pathogenesis and describe its microscopic features.
- ❏ Identify skin lesions related to sun exposure and describe the pathological features of each.
- ❏ Bowen's disease (Squamous cell carcinoma in-situ).
- ❏ Analyze and diagnose a pathologic condition based on a given clinical data.

Diseases of the Skin

Acute inflammatory dermatosis:

1- **Urticaria:** (Immediate type-I hypersensitivity reaction).

Gross lesions: erythematous, oedematous and pruritic plaques.

Microscopic:

- Mild, superficial perivascular mononuclear cells, rare neutrophils and eosinophils with superficial dermal oedema.
- Lesions develop and fade within hours. Persistent lesions are due to urticarial vasculitis.

2- **Eczematous dermatitis:**

Acute eczematous dermatitis: (=spongiotic dermatitis; contact, atopic, drug-related, irritant....etc.)

Gross lesions: Itchy, oozing red papules with vesicles and bullae, ending in scaling plaques.

Microscopic: Intercellular epidermal oedema (spongiosis), with separation of keratinocytes and stretching of intercellular bridges, oedema in the dermal papillae, with superficial perivascular lymphocytic infiltrate and few eosinophils (in drug-related cases).

NB: In chronic eczematous dermatitis, scratching and rubbing of lesions result in acanthosis (increased epidermal thickening) and hyperkeratosis (thickened stratum corneum). Spongiosis and vesicles disappear.

3- **Erythema multiforme:**

Gross lesions: Multiforme means wide diversity of lesions, including macules, papules, vesicles and bullae.

Microscopic:

- Hydropic degeneration of basal keratinocytes, with many lymphocytes along the dermoepidermal junction (interface dermatitis).
- Apoptotic individual keratinocytes.
- Dermal oedema with superficial perivascular lymphocytic infiltrate.

Chronic inflammatory dermatosis:

1) **Psoriasis:** It is a multifactorial immunologic disease that can be induced by local trauma.

Gross lesions: Widespread, well-demarcated, erythematous plaques, covered by loosely adherent silver-white scales (Fig.14.1a).

Microscopic:

- Marked acanthosis, with regular elongation of rete ridges.
- Extensive parakeratotic scale, with loss of granular layer.
- Thinning of epidermis overlying tips of dermal papillae.
- Dilated and tortuous blood vessels within dermal papillae; causing multiple punctuate bleeding points when the scale is removed.
- Neutrophils form small aggregates within spongiotic superficial epidermis (spongiform pustule) and the parakeratotic stratum corneum (Munro's microabscess) (Fig.14.1b).

2) **Lichen planus:**

Gross lesions: Pruritic, violaceous, flat-topped papules having white, lace-like markings referred to as Wickham striae.

Microscopic: (it is a prototypical interface dermatitis)

- Irregular acanthosis, with irregular elongation of rete ridges (saw-tooth pattern).
- Hyperkeratosis and focal hypergranulosis (V-shaped).
- Dense, band-like lymphocytic infiltrate along the dermo-epidermal junction, causing atrophy or necrosis of basal cells;
- Colloid bodies are round, anucleated, deeply eosinophilic apoptotic cells in the basal cell layer or in papillary dermis.

3) **Lichen simplex chronicus:**

Gross lesions: Raised, erythematous, scaly, indurated skin lesions, resulting from continuous rubbing of any pruritic lesion.

Microscopic:

- Hyperkeratosis, acanthosis with elongation of rete ridges and hypergranulosis,
- Fibrosis of dermal papillae, vascular ectasia and dermal chronic inflammatory infiltrate.

Infectious dermatosis:

1) **Bacterial infections:**

Impetigo: Superficial bacterial infection in children, caused by Staph. Aureus or Strept. pyogenes.

Gross lesions: Begins as a single, small macule, rapidly evolving into larger lesion with crust of dried serum.

Microscopic:

- Accumulation of neutrophils beneath stratum corneum (subcorneal pustule).
- Superficial perivascular infiltrate of neutrophils, with neutrophilic exocytosis (epidermal intercellular neutrophils in areas of spongiosis).

2) **Fungal infections:**

Gross lesions: Superficial infections (e.g. Candida) produce pruritic erythematous macules with scales, while deeper infections produce erythematous nodular lesions with focal haemorrhage.

Microscopic:

- Superficial infections show mild eczematous dermatitis, with intraepidermal neutrophils.
- Deeper infections produce tissue damage with granulomatous reaction.
- PAS stain helps in identifying the fungal organisms.

3) **Viral infections:**

Verruca vulgaris:

Gross lesions: Greyish-white to tan, dome-shaped papule, 0.1 to 1cm, with a rough surface.

Microscopic:

- Marked acanthosis, papillomatosis, with inward bending of rete ridges towards the center of the lesion.
- Parakeratotic tires of stratum corneum overlying papillomatous crests, with underlying hypogranulosis.
- Hypergranulosis, with prominent keratohyaline granules in the valleys between papillomatous elevations.
- Cytoplasmic vacuolization (koilocytosis), involving superficial epidermal layers, producing halos of pallor around infected nuclei.
- Dilated blood vessels within papillary dermis (*Fig.14.2*).

Blistering (bullous) disorders:

1) **Pemphigus vulgaris:**

A rare autoimmune disorder, caused by antibody-mediated (type II) hypersensitivity reaction, with uniform deposition of immunoglobulin

Diseases of the skin
(IgG) and complement along cell membrane of keratinocytes, causing lysis of adhesive junctions between neighbouring keratinocytes (acantholysis).

Gross lesions: Superficial, flaccid vesicles and bullae that rupture easily, leaving deep and extensive erosions.

Microscopic:

- Intraepidermal, suprabasal blister; basal cells remain attached having the tomb-stone-like pattern forming the floor.
- Blister cavity contains eosinophils and round acantholytic cells.
- Upper dermis shows superficial perivascular lymphocytes and eosinophils (Fig.14.3).

2) **Bullous pemphigoid:**

An acquired blistering disease, with an autoimmune basis, caused by linear deposition of IgG antibody outlining the subepidermal basement membrane zone.

Gross lesions: Tense bullae, filled with clear fluid, on normal or erythematous skin; do not rupture easily.

Microscopic (Fig.14.4):

- Subepidermal non-acantholytic blisters; its roof is made of full-thickness epidermis with intact intercellular junctions and the cavity contains numerous eosinophils.
- Upper dermis shows a perivascular infiltrate of lymphocytes and few eosinophils with neutrophils.
- Eosinophilic papillary microabscess.
- Superficial dermal oedema and basal cell layer vacuolization.

3) **Dermatitis herpetiformis:**

An autoimmune, blistering disorder, showing selective deposition of IgA autoantibody at the tips of dermal papillae.

Gross lesions: Bilateral, symmetrical and grouped, extremely pruritic, intact and eroded, erythematous blisters.

Microscopic:

- Neutrophils accumulate at the tips of dermal papillae, forming small papillary microabscesses.
- Overlying basal cells show vacuolization and focal dermoepidermal separation that coalesce to form true subepidermal blister.

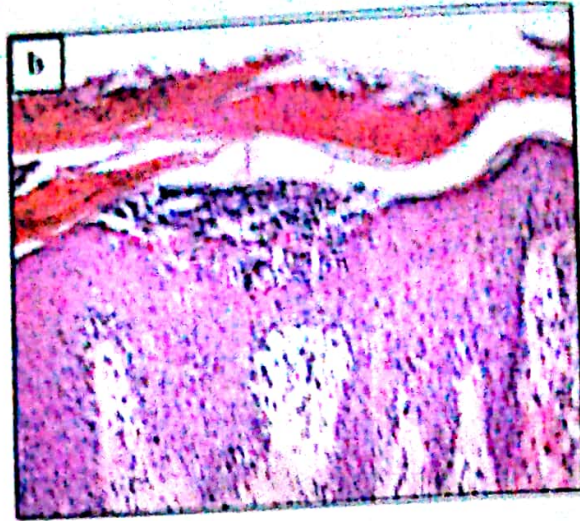


Fig.14.1: Psoriasis (a) Skin lesions (b) Microscopic; note Munro's microabscess

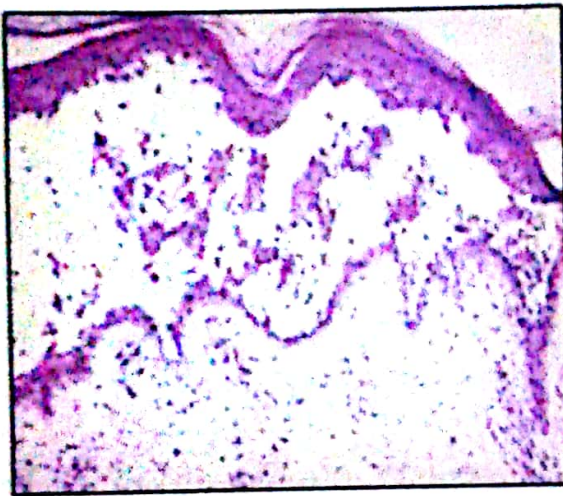


Fig.14.2: Pemphigus vulgaris.

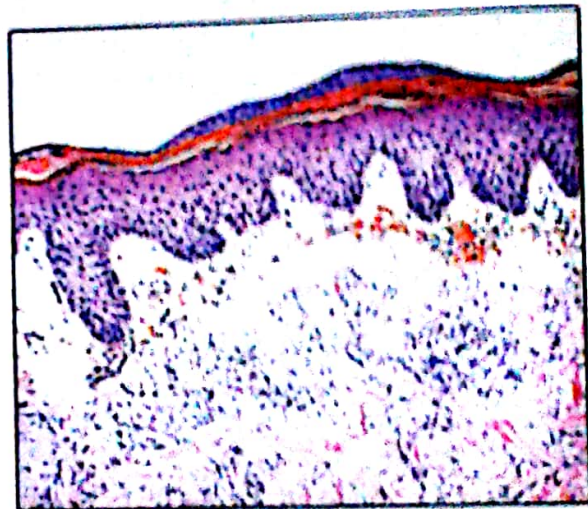


Fig.14.3: Bullous pemphigoid

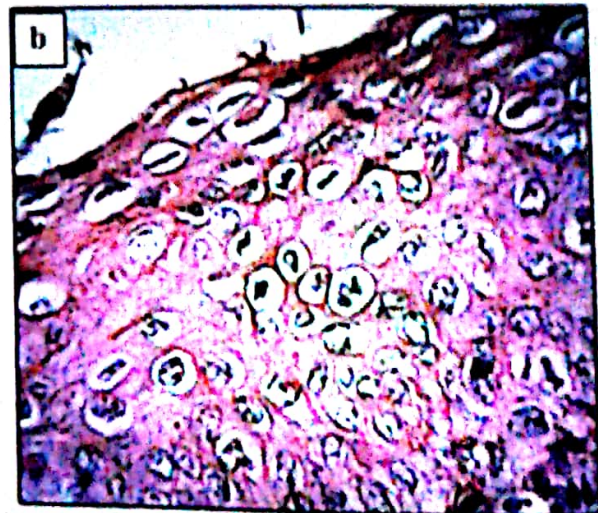


Fig.14.4: Verruca vulgaris (a) Low power (b) Note HPV Koilocytes in the upper epithelium

Benign and malignant epithelial lesions

1) **Seborrheic keratosis:**

A common benign pigmented epidermal tumor, occur in middle-aged or older persons, more common on the trunk; but extremities, head and neck are also involved.

Gross: Round, exophytic, dark-brown, coin-like plaques, varying in size from millimeters to centimeters, having a stuck-on appearance and rough, granular appearing surface.

Microscopic:

- Hyperkeratosis, acanthosis and papillomatosis.
- This lesion is purely epidermal. It is made-up of monotonous sheets of basaloid cells, showing variable melanin pigmentation with small keratin-filled cysts and pseudohorn cysts (Fig.14.5).



Fig.14.5: Seborrheic keratosis.

2) **Actinic keratosis:** (Sun-induced dysplasia of keratinocytes)

Gross: Multiple, scaly erythematous patches, having rough surface, occur in sun-exposed areas in fair-skinned people.

Microscopic:

- Hypertrophic variant shows psoriasiform epidermal hyperplasia, orthokeratosis alternating with parakeratosis and mild dysplasia confined to the basal cell layer.
- Bowenoid variant shows full thickness squamous atypia with loss of orderly arrangement of the epidermis.

- The dermis shows actinic elastosis and chronic inflammatory cellular infiltrate.

3) **Bowen's disease** (*Squamous cell carcinoma in-situ*)

Gross: Scaly erythematous plaques on sun-exposed skin in elderly patients.

Microscopic: (patterns: psoriasiform, atrophic, verrucous....etc.)

- Full thickness dysplasia of epidermal cells with mitotic figures, multinucleated cells and dyskeratosis.
- Pilosebaceous epithelium may be involved by atypical keratinocytes.
- Parakeratosis with loss of granular layer.
- Dermal inflammation.

Malignant epithelial tumours:

Squamous cell carcinoma and basal cell carcinoma. See general pathology.

Melanocytic proliferations:

- 1- **Melanocytic nevi:** are benign congenital or acquired neoplasm of melanocytes.

Gross: Tan to brown, uniformly pigmented, small papules (5 mm or less), having well-defined rounded borders.

Microscopic:

- a- **Junctional nevi:** Nests of round to oval cells, growing along the dermoepidermal junction, having uniform, round nuclei, inconspicuous nucleoli with little or no mitotic activity.
- b- **Compound nevi:** Nests and cords of nevus cells grow from the junctional zone into the underlying dermis.
- c- **Intradermal nevi:** Junctional component disappear and nevus cells appear intradermal only showing maturation; i.e., superficial cells are large, melanized and grow in nests; deeper cells are smaller, having no melanin and grow in cords or single cells. The deepest cells have fusiform contour and grows in fascicles.

- 2- **Dysplastic nevi:**

Gross: Are larger and numerous; appear as flat macules or slightly raised plaques, having variable pigmentation and irregular borders.

Microscopic:

Appear as compound nevi having junctional and dermal components.

- Junctional component shows large cell nests exhibiting fusion and bridging with adjacent nests.

Nevus cells show irregular angulated hyperchromatic nuclei.

- The dermal component shows sparse lymphocytic infiltrate, melanin incontinence and linear fibrosis surrounding epidermal nests of melanocytes.

3- **Melanoma:**

A malignant tumour, its incidence is highest in areas where sun exposure is high and much of population is fair-skinned.

Gross: A nodule, with striking variations in pigmentation, including shades of black, brown, red, dark blue and grey, with irregular notched borders.

Microscopic:

- **Radial growth phase (in situ):** malignant cells grow as poorly formed nests or as individual cells at all levels of the epidermis (pagetoid spread); the dermis shows brisk lymphocytic infiltrate.
- **Vertical growth phase:** the tumor grows downwards into the deeper dermal layers lacking cellular maturation.
- Melanoma cells are large, epithelioid-like or spindle, having large nuclei, with irregular contours, peripheral chromatin clumping and prominent eosinophilic nucleoli.

NB:

- - **Warning signs in a pigmented lesion:**
 - Rapid enlargement in size, irregular borders, itching or pain and variegated colour.
- **Metastasis in melanoma is predicted by:**
 1. Measuring the depth of invasion in millimeters from the top of granular layer (Breslow thickness)
 2. Tumours with high mitotic rate.

SUMMARY

Acute inflammatory dermatosis:

Urticaria: (immediate type-I hypersensitivity reaction)

Eczematous dermatitis.

- Acute eczematous dermatitis.
- Erythema multiforme.

Chronic inflammatory dermatosis:

Psoriasis

Lichen planus

Lichen simplex chronicus

Infectious dermatosis:

Bacterial infections. Impetigo.

Fungal infections

Viral infections, Verruca vulgaris.

Blistering (bullous) disorders:

Pemphigus vulgaris

Bullous pemphigoid

Dermatitis herpetiformis

Benign and malignant epithelial lesions:

Seborrheic keratosis

Actinic keratosis

Bowen's disease (Squamous cell carcinoma in-situ).

Malignant epithelial tumours:

Squamous cell carcinoma and basal cell carcinoma.

Melanocytic proliferations:

Melanocytic nevi: Are benign neoplasm of melanocytes.

Histologic types: Junctional, compound and intradermal nevi.

Dysplastic nevi.

Melanoma: Malignant neoplasm of melanocytes.